1-6 个碳原子。在另一个实施方案中，所述烷基具有 1-4 个碳原子。所述烷基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代(thio)和硫烷基。在一个实施方案中，所述烷基是 CH_3。

在另一个实施方案中，“烯基”指不饱和的烃，包括具有一个或多个双键的直链、支链和环状基团。所述烯基可以具有一个双键、两个双键、三个双键等。烯基的例子是乙烯基、丙烯基、丁烯基、环已烯基等。在一个实施方案中，所述烯基具有 1-12 个碳原子。在另一个实施方案中，所述烯基具有 1-7 个碳原子。在另一个实施方案中，所述烯基具有 1-6 个碳原子。在另一个实施方案中，所述烯基具有 1-4 个碳原子。所述烯基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。

“卤代烷基”指被一个或多个卤素原子取代的如上定义的烷基，在一个实施方案中被 F 取代，在另一个实施方案中被 Cl 取代，在另一个实施方案中被 Br 取代，在另一个实施方案中被 I 取代。

“芳基”指具有至少一个碳环芳族基团或杂环芳族基团的芳族基团，所述芳基可以是未取代的或由一个或多个选自以下的基团取代：卤素、羟基、烷氧羰基、酰胺基、烷基酰胺基、二烷基酰胺基、硝基、氨基、烷氨基、二烷基氨基、羧基、硫代和硫烷基。芳环的非限制性的例子是苯基、萘基、吡喃基、吡咯基、吡嗪基、嘧啶基、吡唑基、吡啶基、呋喃基、苯硫基、噻唑基、咪唑基、异噁唑基等。在一个实施方案中，所述芳基是 4-8 元环。在另一个实施方案中，所述芳基是 4-12 元环。在另一个实施方案中，所述芳基是 6 元环。在另一个实施方案中，所述芳基是 5 元环。在另一个实施方案中，所述芳基是 2-4 个环的稠环体系。

“羟基”指 OH 基。本领域的技术人员应该理解，当 T 是 OR 时，R 不是 OH。

在一个实施方案中，术语“卤素”在一个实施方案中指 F，在另一个实施方案中指 Cl，在另一个实施方案中指 Br，在另一个实施方案中指 I。在

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一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括结晶技术。在另一个实施方案中，所述结晶技术包括对映异构体的分异结晶（differential crystallization）。在另一个实施方案中，所述结晶技术包括非对映的盐（酒石酸盐或奎宁盐）的分异结晶。在另一个实施方案中，所述结晶技术包括手性辅助衍生物（薄荷醇酯等）的分异结晶。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明的外消旋化合物的分离包括使所述外消旋混合物与另一种手性基团反应，形成非对映的混合物，然后分离非对映异构体并除去其它手性基团以得到纯的对映异构体。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括手性合成。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括生物拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括酶法拆分。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括使用手性固定相的色谱分离。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括亲和色谱法。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括毛细管电泳。在另一个实施方案中，所述光学活性的(*R*)异构体或(*S*)对映异构体从本发明化合物的外消旋混合物的分离包括形成手性碳原子的羟基与光学活性的酸（例如(-)-樟脑酸）的酯基，通过分级结晶或优选通过快速色谱法（flash-chromatography）分离由此获得的非对映异构体的酯，然后将各单独的酯水解为醇。

在另一个实施方案中，通过本发明的方法或通过本发明的外消旋混合物的手性分离所获得的对映异构体的纯度和选择性可以通过 HPLC 分析来测定。

在另一个实施方案中，所述方法还包含将式(I)的化合物转化为其异构体、代谢产物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合的步骤。

应该理解，所述方法可以包括本文所述的任何实施方案，本领域的技

术人员会理解，所述实施方案会适于制备对应式的化合物。

在一些实施方案中，本文所述的化合物用于预防和治疗肌萎缩症、骨相关的病症和与糖尿病相关的病症。

在一些实施方案中，本文所述的化合物可单独地或作为组合物用于治疗雄性和雌性的各种激素相关的病症，例如性腺功能减退症、少肌症、勃起障碍、缺乏性欲、骨质疏松症和能育性（fertility）。在一些实施方案中，本文所述的化合物用于刺激或促进或恢复对多种过程的功能，这继而导致治疗本文所述的病症，尤其包括促进红细胞生成、骨发生、肌肉生长、葡萄糖摄取、胰岛素分泌，和/或预防脂质生成、凝血、胰岛素抵抗、动脉粥样硬化、破骨细胞活性等。

在一个实施方案中，本发明的方法利用所述化合物与受体接触或结合，并由此介导所述的效应。在一些实施方案中，所述受体是核受体，在一个实施方案中，所述核受体是雄激素受体，或者在另一个实施方案中是雌激素受体，或者在另一个实施方案中是孕酮受体，或者在另一个实施方案中是糖皮质激素受体。在一些实施方案中，所述多种效应可以作为与个体的多种受体结合的功能而同时发生。在一些实施方案中，本文所述的化合物的组织选择性效应提供对不同靶器官的同时作用。

药物组合物

在一些实施方案中，本发明提供使用的方法，所述方法包括给药含有所述化合物的组合物。如本文使用的，“药物组合物”指“治疗有效量”的活性成分（即式 I 的化合物），与药学上可接受的载体或稀释剂。如本文使用的，“治疗有效量”指对于给定的病症和给药方案提供疗效的量。

如本文使用的，术语“给药”指使个体与本发明的化合物接触。如本文使用的，给药可以在体外（即试管内）或体内（即活的有机体例如人类的细胞或组织）中进行。在一个实施方案中，本发明包括向个体给药本发明的化合物。

含有本发明化合物的药物组合物可以通过本领域技术人员已知的任何方法向个体给药，例如口服、肠胃外、血管内、癌旁、经粘膜、经皮、肌内、鼻内、静脉内、皮内、皮下、舌下、腹膜内、心室内、颅内、阴道内给药，通过吸入、经直肠、瘤内给药，或者通过其中重组病毒/组合物能被

递送至组织的任何方法（例如穿刺针（needle）或导管）给药。或者，对于向粘膜细胞施用、皮肤或眼睛施用，可能需要局部施用。另一种给药的方法是经吸入剂或气雾剂。

在一个实施方案中，所述药物组合物口服给药，因此它被配制成适合口服给药的形式，即作为固体或液体制剂。合适的固体口服制剂包括片剂、胶囊、丸剂、颗粒剂、小丸（pellets）、散剂等。合适的液体口服制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在本发明的一个实施方案中，所述 SARM 化合物被配制在胶囊中。根据该实施方案，本发明的组合物除含有本发明的化合物和惰性载体或稀释剂之外，还含有硬胶囊。

在一个实施方案中，所述微粒化的胶囊包含含有本发明化合物的颗粒，其中，本文使用的术语“微粒化”指粒径小于 100 微米的颗粒，或者在另一个实施方案中，指粒径小于 60 微米的颗粒，或者在另一个实施方案中，指粒径小于 36 微米的颗粒，或者在另一个实施方案中，指粒径小于 16 微米的颗粒，或者在另一个实施方案中，指粒径小于 10 微米的颗粒，或者在另一个实施方案中，指粒径小于 6 微米的颗粒。

而且，在另一个实施方案中，所述药物组合物通过静脉内、动脉内或肌内注射液体制剂来给药。合适的液体制剂包括溶液剂、混悬剂、分散剂、乳剂、油剂等。在一个实施方案中，所述药物组合物经静脉内给药，因此被配制成适合静脉内给药的形式。在另一个实施方案中，所述药物组合物经动脉内给药，因此被配制成适合动脉内给药的形式。在另一个实施方案中，所述药物组合物肌内给药，因此被配制成适合肌内给药的形式。

而且，在另一个实施方案中，所述药物组合物局部施用于身体表面，因此被配制成适合局部施用的形式。合适的局部制剂包括凝胶剂、软膏、乳剂、洗剂、滴剂等。对于局部施用，本发明的化合物或其生理上耐受的衍生物（例如盐、酯、*N*-氧化物等）被制成在具有或不具有药用载体的生理上可接受的稀释剂中的溶液剂、混悬剂或乳剂，并以这些形式施用。

而且，在另一个实施方案中，所述药物组合物作为栓剂（例如直肠栓剂或尿道栓剂）来给药。而且，在另一个实施方案中，所述药物组合物通过皮下埋植小丸来给药。在另一个实施方案中，所述小丸在一段时间内提供本文所述化合物的控制释放。在另一个实施方案中，所述药物组合物经

阴道给药。

在另一个实施方案中，活性化合物可以在小囊泡、特别是脂质体中递送(参见Langer, Science 249:1627-1633 (1990); Treat等人,于Liposomes in the Therapy of Infectious Disease and Cancer, Lopez- Berestein和Fidler (著者), Liss, New York, pp. 363-366 (1989); Lopez-Berestein, 出处同上, pp. 317-327; 一般地参见出处同上)。

如本文使用的，“药学上可接受的载体或稀释剂”是本领域技术人员熟知的。所述载体或稀释剂可以是用于固体制剂的固体载体或稀释剂、用于液体制剂的液体载体或稀释剂、或它们的混合物。

固体载体/稀释剂包括但不限于胶质、淀粉（例如玉米淀粉、预糊化淀粉（pregeletanized starch））、糖（例如乳糖、甘露醇、蔗糖、葡萄糖）、纤维素材料（例如微晶纤维素）、丙烯酸酯（例如聚甲基丙烯酸酯）、碳酸钙、氧化镁、滑石或它们的混合物。

在一个实施方案中，本发明的组合物可以包括本发明的化合物或其与一种或多种药学上可接受的赋形剂任意组合。

应该理解，本发明包括本文所述化合物（在一些实施方案中被称为“本发明的化合物”）的任何实施方案。

根据本发明的实施方案，合适的赋形剂和载体可以是固体或液体，其类型一般根据使用的给药类型来选择。脂质体也可以用于递送所述组合物。合适的固体载体的例子包括乳糖、蔗糖、明胶和琼脂。口服剂型可以含有合适的粘合剂、润滑剂、稀释剂、崩解剂、着色剂、调味剂、流动诱导剂（flow-inducing agent）和熔解剂。液体剂型可以含有例如合适的溶剂、防腐剂、乳化剂、助悬剂、稀释剂、甜味剂、增稠剂和熔解剂。肠胃外和静脉内形式还应该包含矿物质和其它材料以便使得它们与所选的注射或递药系统的类型相容。当然，也可以使用其它赋形剂。

对于液体制剂，药学上可接受的载体可以是含水的或非水溶液、悬浮液、乳液或油。非水性溶剂的例子是丙二醇、聚乙二醇和可注射的有机酯类例如油酸乙酯。含水载体包括水、醇/水溶液、环糊精、乳液或悬浮液，包括盐水和缓冲介质。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

肠胃外载体（用于皮下、静脉内、动脉内或肌内注射）包括氯化钠溶液、林格氏葡萄糖、葡萄糖和氯化钠、乳酸林格和固定油。静脉内载体包括流体和营养补充剂、电解质补充剂（例如基于林格氏葡萄糖的电解质补充剂）等。其例子是无菌液体，例如加入和未加入表面活性剂和其它药学上可接受的助剂的水和油。通常，水、盐水、葡萄糖水溶液和相关的糖溶液以及二醇例如丙二醇或聚乙二醇是优选的液体载体，特别是对于可注射溶液剂。油的例子是石油、动物油、植物油或合成来源的油，例如，花生油、大豆油、矿物油、橄榄油、向日葵油和鱼肝油。

而且，所述组合物还可以包含粘合剂（例如阿拉伯胶、玉米淀粉、明胶、卡波姆、乙基纤维素、瓜尔胶、羟丙基纤维素、羟丙基甲基纤维素、聚维酮），崩解剂(例如玉米淀粉、马铃薯淀粉、藻酸、二氧化硅、交联羧甲基纤维素钠（croscarmelose sodium）、交聚维酮、瓜尔胶、羟基乙酸淀粉钠)，各种 pH 和离子强度的缓冲剂(例如 Tris-HCl、醋酸盐、磷酸盐)，防止吸附到表面的添加剂例如白蛋白或明胶，洗涤剂(例如 Tween 20、Tween 80、Pluronic F68、胆汁酸盐)，蛋白酶抑制剂，表面活性剂（例如十二烷基硫酸钠)，渗透促进剂，增溶剂(例如克列莫佛(cremophor)、甘油、聚乙烯甘油(polyethylene glycerol)、苯扎氯铵、苯甲酸苄酯、环糊精、失水山梨糖醇(sobitan)酯、硬脂酸)，抗氧化剂(即抗坏血酸、偏亚硫酸氢钠、丁基化羟基苯甲醚（butylated hydroxyanisole）），稳定剂(例如羟丙基纤维素、羟丙基甲基纤维素)，增黏剂(例如卡波姆、胶体二氧化硅、乙基纤维素、瓜尔胶)，甜味剂(例如天冬甜素、柠檬酸)，防腐剂(例如 Thimerosal、苄醇、对羟苯甲酸酯)，着色剂，润滑剂(例如硬脂酸、硬脂酸镁、聚乙二醇、十二烷基硫酸钠)，助流剂(例如胶体二氧化硅)，增塑剂(例如邻苯二甲酸二乙酯、柠檬酸三乙酯)，乳化剂(例如卡波姆、羟丙基纤维素、十二烷基硫酸钠)，聚合物包衣（例如泊洛沙姆或泊洛沙胺（poloxamines））、包衣剂和成膜剂(例如乙基纤维素、丙烯酸酯、聚甲基丙烯酸酯)和/或辅剂。

在一个实施方案中，本文提供的药物组合物是控释组合物，即在该组合物中，本发明的化合物在给药后的一段时间内释放。控释或缓释组合物包括亲脂性贮库（depots）（例如脂肪酸、蜡、油）中的制剂。在另一个实施方案中，所述药物组合物是速释组合物，即在该组合物中全部量的化合

物在给药后立即释放。

在另一个实施方案中，所述药物组合物可以在控释系统中递送。例如，所述药剂可以使用静脉输注、可植入渗透泵、透皮贴剂、脂质体或其它给药方式给药。在一个实施方案中，可以使用泵(参见 Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald 等人, Surgery 88:607 (1980); Saudek 等人, N. Engl. J. Med. 321:674 (1989))。在另一个实施方案中，可以使用聚合物材料。在另一个实施方案中，可以将控释系统置于治疗靶（即脑）附近，因此仅需要全身剂量的一部分(参见例如 Goodson, 于 Medical Applications of Controlled Release, supra, vol. 2, pp. 116-138 (1984))。在 Langer 的一篇综述 (Science 249:1627-1633 (1990))中讨论了其它控释系统。

所述组合物也可以包括在聚合的化合物，例如聚乳酸、聚乙醇酸、水凝胶等的粉粒制剂之中或之上，或在脂质体、微乳、微胶粒、单层或多层小囊泡、血影或原生质球之上引入活性材料。这种组合物会影响物理状态、溶解性、稳定性、体内释放率和体内清除率。

本发明还包括包被聚合物(例如泊洛沙姆或泊洛沙胺)和与直接抗组织特异性受体、配体或抗原的抗体偶联或与组织特异性受体的配体偶联的化合物的微颗组合物。

本发明还包括通过水溶性聚合物，例如聚乙二醇、聚乙二醇和聚丙二醇的共聚物、羧甲基纤维素、葡聚糖、聚乙烯醇、聚乙烯吡咯烷酮或聚脯氨酸的共价连接而修饰的化合物。已知所述修饰的化合物在静脉注射后显示出比相应的未修饰化合物长得多的血液半衰期（Abuchowski 等人, 1981; Newmark 等人, 1982;和 Katre 等人, 1987）。这种修饰也可以增加所述化合物在水溶液中的溶解度、消除聚集、提高所述化合物的物理和化学稳定性，并大大降低所述化合物的免疫原性和反应性。因此，与未修饰的化合物相比，通过更低频率地或更小剂量地给药这种聚合物-化合物衍生物，可以实现期望的体内生物活性。

含有活性组分的药物组合物的制备在本领域中很好理解，例如通过混合、造粒或压片的方法。活性治疗成分经常与药学上可接受的并与所述活性成分相容的赋形剂混合。对于口服给药，本发明的化合物或它们的生理上耐受的衍生物例如盐、酯、*N*-氧化物等与为此目的惯用添加剂例如载体、

稳定剂或惰性稀释剂混合，并以常规方法转化为适合给药的形式，例如片剂、包衣片剂、硬或软胶囊、水溶液、醇溶液或油溶液剂。对于肠胃外给药，本发明的化合物或它们生理上耐受的衍生物例如盐、酯、*N*-氧化物等被转化为溶液剂、混悬剂或乳剂（如果需要，用为此目的的惯用的、合适的物质，例如增溶剂等）。

活性组分可以作为中性的药学上可接受的盐的形式被配制成组合物。药学上可接受的盐包括酸加成盐（由多肽或抗体分子的自由氨基形成），其由无机酸例如盐酸或磷酸、或有机酸例如乙酸、草酸、酒石酸、扁桃酸等形成。由自由羧基形成的盐也可以得自无机碱，例如氢氧化钠、氢氧化钾、氢氧化铵、氢氧化钙或氢氧化铁，以及有机碱，例如异丙胺、三甲胺、2-乙胺基乙醇、组氨酸、普鲁卡因等。

为了用于药物，所述化合物的盐是药学上可接受的盐。但是，其它盐也可用于本发明化合物或其药学上可接受的盐的制备中。合适的本发明化合物的药学上可接受的盐包括酸加成盐，其可以通过例如将本发明化合物的溶液与药学上可接受的酸的溶液混合来形成，所述酸例如盐酸、硫酸、甲磺酸、富马酸、马来酸、琥珀酸、乙酸、苯甲酸、草酸、柠檬酸、酒石酸、碳酸或磷酸。

在一个实施方案中，本发明提供包含本发明的化合物的药物组合物。在一个实施方案中，这种组合物用于口服睾酮替代疗法。

在一个实施方案中，本发明还提供包含两种或多种本发明的化合物或它们的多晶型物、异构体、水合物、盐、*N*-氧化物等的组合物。本发明还涉及组合物和药物组合物，所述药物组合物单独包含本发明的化合物，或者包含本发明的化合物与孕激素或雌激素的组合，或者在另一个实施方案中，包含本发明的化合物与化疗化合物、成骨化合物或生肌化合物、或其它适合本文所述的应用的药剂的组合。在一个实施方案中，本发明的组合物包含合适的载体、稀释剂或盐。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 0.1-200 mg/天的剂量给药本发明的化合物。在一个实施方案中以 0.1-10 mg 的剂量、或在另一个实施方案中以 0.1-26 mg 的剂量、或在另一个实施方案中以 0.1-60 mg 的剂量、或在另一

个实施方案中以 0.3-16 mg 的剂量，或在另一个实施方案中以 0.3-30 mg 的剂量、或在另一个实施方案中以 0.6-26 mg 的剂量、或在另一个实施方案中以 0.6-60 mg 的剂量、或在另一个实施方案中以 0.76-16 mg 的剂量、或在另一个实施方案中以 0.76-60 mg 的剂量、或在另一个实施方案中以 1-6 mg 的剂量、或在另一个实施方案中 1-20 mg 的剂量、或在另一个实施方案中以 3-16 mg 的剂量、或在另一个实施方案中以 30-60 mg 的剂量、或在另一个实施方案中以 30-76 mg 的剂量、或在另一个实施方案中以 100-2000 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明的方法可以包括以各种剂量给药本发明的式 I 化合物。在一个实施方案中，以 1 mg 的剂量给药本发明的化合物。在另一个实施方案中，以 3 mg、6 mg、10 mg、16 mg、20 mg、26 mg、30 mg、36 mg、40 mg、46 mg、50 mg、56 mg、60 mg、66 mg、70 mg、76 mg、80 mg、86 mg、90 mg、96 mg 或 100 mg 的剂量给药本发明的化合物。

在一个实施方案中，本发明提供使用方法，该方法包括给药包含以下各项的药物组合物：a) 本文所述的任何实施方案的化合物；和 b) 药学上可接受的载体或稀释剂；所述组合物应理解为包含本文所述化合物的类似物、异构体、代谢产物、衍生物、药学上可接受的盐、*N*-氧化物、水合物或它们的任意组合，并且可以包含式 I 的化合物。

在一些实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 药学上可接受的载体或稀释剂；c) 助流剂；和 d) 润滑剂。

在另一个实施方案中，本发明提供药物组合物的使用方法，该药物组合物包含：a) 本文所述的任何实施方案的化合物，包括其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、*N*-氧化物、水合物或它们的任意组合；b) 乳糖一水合物；c) 微晶纤维素；d) 硬脂酸镁；和 e) 胶体二氧化硅。

在一些实施方案中，本发明的方法利用包含本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提

供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是含水或非水溶液、混悬剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，本发明的方法利用含有本发明的化合物的组合物，所述方法的优点是所述化合物是雄激素受体的非类固醇类配体并在体内显示出合成代谢活性。根据这个方面，这种化合物不伴有严重的副作用，提供方便的给药方式和较低的生产成本，并且口服可生物利用，与其它不希望的类固醇受体没有显著的交叉反应性，并且可能具有很长的生物半衰期。

当施用于哺乳动物，特别是人时，预计医师会确定最适合个体的实际剂量和治疗时间，并且可以根据具体个体的年龄、体重和应答而变化。

在一个实施方案中，用于给药的组合物可以是无菌溶液剂，或者在其它实施方案中，可以是水性或非水性的溶剂、悬混剂或乳剂。在一个实施方案中，所述组合物可以包含丙二醇、聚乙二醇、可注射的有机酯例如油酸乙酯、或环糊精。在另一个实施方案中，组合物也可以包含湿润剂、乳化剂和/或分散剂。在另一个实施方案中，所述组合物也可以包含无菌水或任何其它无菌可注射介质。

在一个实施方案中，本发明提供用于如本文所述的本发明的任何方法

的化合物和组合物（包括本文所述的任意实施方案）。在一个实施方案中，使用本发明的化合物或含有它的组合物会有利于抑制、压制除、增强或促进个体体内所期望的应答，这一点本领域的技术人员会理解。在另一个实施方案中，所述组合物还可以含有其它活性成分，其活性对给药本发明的化合物所针对的具体应用是有用的。

在一些实施方案中，所述组合物还含有 5α-还原酶抑制剂（5ARI）、一种或多种 SARM、选择性雌激素受体调节剂（SERM）、芳香酶抑制剂（例如但不局限于阿那曲唑（anastrazole）、依西美坦或来曲唑）、GnRH 激动剂或拮抗剂、类固醇或非类固醇 GR 配体、类固醇或非类固醇 PR 配体、类固醇或非类固醇 AR 配体、17-醛酮还原酶抑制剂或 17β-羟基类固醇脱氢酶抑制剂。在一些实施方案中，这种组合物可以用于治疗激素依赖性病症，例如不育、激素反应性癌例如生殖腺癌或泌尿生殖器癌的瘤形成。

在一些实施方案中，所述组合物包含本文所述的化合物和另一种治疗性化合物，尤其包括 5ARI，例如非那雄胺、度他雄胺、艾宗特来；其他 SARM，例如，RU-58642、RU-56279、WS9761 A 和 B、RU-59063、RU-58841、贝氯特来、LG-2293、L-245976、LG-121071、LG-121091、LG-121104、LGD-2226、LGD-2941、LGD-3305、YM-92088、YM-175735、LGD-1331、BMS-357597、BMS-391197、S-40503、BMS-482404、EM-4283、EM-4977、BMS-564929、BMS-391197、BMS-434588、BMS-487745、BMS-501949、SA-766、YM-92088、YM-580、LG-123303、LG-123129、PMCol、YM-175735、BMS-591305、BMS-591309、BMS-665139、BMS-665539、CE-590、116BG33、154BG31、arcarine、ACP-105；SERM，例如，三苯氧胺（tamoxifene）、4-羟三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬（ospemifene）、屈洛昔芬、雷诺昔芬、阿佐昔芬，巴多昔芬（bazedoxifene）、PPT (1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑)、DPN (二芳基丙腈)、拉索昔芬、哌喷昔芬(pipendoxifene)、EM-800、EM-652、萘福昔定、秦唑昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬（enclomiphene）、地马孕酮醋酸盐、

DPPE、(*N,N*-二乙基-2-{4-(苯基甲基)-苯氧基}乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞(prinaberel)、ERB-041、WAY-397、WAY-244、ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F]FEDNP、LSN-500307、AA-102、半枝莲(Ban zhi lian)、CT-101、CT-102、VG-101；GnRH 激动剂或拮抗剂，例如，亮丙瑞林、戈舍瑞林、曲普瑞林、阿法前列醇、组氨瑞林、地肽瑞里、加尼瑞克、安肽伊妥瑞克、西曲瑞克、雷莫瑞克、加尼瑞克、安雷利克斯、替维瑞克、阿巴瑞克、奥扎瑞克(ozarelix)、舒伐格瑞克(sufugolix)、普拉瑞克、地加瑞克(degarelix)、NBI-56418、TAK-810、脂酰基碱(acyline)；FSH 激动剂或拮抗剂、LH 激动剂/拮抗剂、芳香酶抑制剂，例如来曲唑、阿那曲唑、阿他美坦、法倔唑、米那美坦、依西美坦、普洛美坦、利阿唑、NKS-01、伏氯唑、YM-51、芬罗唑、4-羟雄烯二酮、氨基苯乙哌啶酮(aminogluethimide)、罗谷亚胺；类固醇或非类固醇糖皮质激素受体配体，例如，ZK-216348、ZK-243149、ZK-243185、LGD-5552、米非司酮、RPR-106541、ORG-34517、GW-215864X、Sesquicillin、CP-472555、CP-394531、A-222977、AL-438、A-216054、A-276575、CP-394531、CP-409069、UGR-07；类固醇或非类固醇孕酮受体配体；类固醇或非类固醇 AR 拮抗剂，例如氟他胺、羟基氟他胺、比卡鲁胺、尼鲁米特，羟基类固醇脱氢酶抑制剂，PPARα配体例如苯扎贝特、非诺贝特、吉非贝齐；PPARγ配体，例如，达格列酮、吡格列酮、罗格列酮、伊格列酮(isaglitazone)、利格列酮(rivoglitazone)、萘格列酮(netoglitazone)；双重作用的 PPAR 配体，例如，naveglitazar、法格立他扎、替格列扎(tesaglitazar)、拉格列扎(ragaglitazar)、奥格列扎(oxeglitazar)、PN-2034、PPAR δ；17-酮还原酶抑制剂，3β-DHΔ4,6-异构酶抑制剂，3β-DHΔ4,5-异构酶抑制剂，17,20 碳链酶抑制剂，p450c17 抑制剂，p450ssc 抑制剂，17,20 裂合酶抑制剂，或它们的组合。

应该理解，以上给药两种或多种药剂的任何方法、计时、途径或它们的组合应被认为由本文所述的短语“联合给药”所包含。

在一个实施方案中，本发明提供患癌个体的骨骼相关事件(SRE)的治

疗、预防、压制或抑制、或降低罹患它的风险，其包括给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合，所述骨骼相关事件(SRE)例如骨折、骨手术、骨辐射、脊髓压迫症、新生骨转移、骨丢失或它们的组合。本发明特别涉及用式(I)的化合物治疗正在进行或已经进行雄激素剥夺治疗(ADT)的罹患前列腺癌个体的 SRE。

在一个实施方案中，用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件是骨折，在一个实施方案中，所述骨折是病理性骨折、非创伤性骨折、脊椎骨折、非脊椎骨折、形态测定骨折（morphometric fractures）或它们的组合。在一些实施方案中，骨折可以是闭合骨折、复合骨折、横骨折、青枝骨折或粉碎性骨折。在一个实施方案中，发生骨折的可以是身体的任何骨，在一个实施方案中，所述骨折是臂、腕、手、指、腿、踝、足、趾、髋、锁骨的任意一块或多块骨中的骨折或它们的组合。

在另一个实施方案中，本文提供的方法和/或组合物有效地治疗、预防、压制、抑制骨骼相关事件、或降低其风险，所述骨骼相关事件例如病理性骨折、脊髓压迫症、高钙血症多、骨相关的疼痛或它们的组合。

在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括必要的骨手术和/或骨辐射，其在一些实施方案中，用于治疗在一个实施方案中由骨损害或神经压迫引起的疼痛。在另一个实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括个体的脊髓压迫症，或有必要改变抗肿瘤疗法，包括改变激素疗法。在一些实施方案中，力求用本文提供的方法和/或利用本文提供的组合物治疗的骨骼相关事件包括治疗、压制、预防骨转移或骨丢失、降低其发病率或延缓其进展或严重性。在一个实施方案中，骨丢失可以包括骨质疏松症、骨质减少或它们的组合。在一个实施方案中，骨骼相关事件可以包括本文所列的实施方案的任意组合。

在一个实施方案中，本文提供的方法和/或利用本文提供的组合物有效地减少骨转移，例如在病灶数量、病灶大小或它们的组合方面。根据本发明的这一方面，在一个实施方案中，本文提供一种预防或抑制个体癌症向骨转移的方法，所述包括向所述个体给药包含托瑞米芬、雷洛昔芬、他莫

昔芬或其类似物、功能衍生物、代谢产物或它们的组合、或它们的药学上可接受的盐的组合物的步骤。在一个实施方案中，所述代谢产物可以包括奥培米芬、非培米芬（fispemifene）或它们的组合。在一个实施方案中，所述癌症是前列腺癌。

在一个实施方案中，所述骨骼相关事件是癌症治疗的结果。在一个实施方案中，所述骨骼相关事件是激素剥夺治疗的结果，而在另一个实施方案中，它们是雄激素剥夺治疗(ADT)的结果。

在一个实施方案中，本发明的化合物用于预防或逆转雄激素剥夺治疗(ADT)引起的副作用，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD 降低和/或骨量减少。

在雄性，尽管成熟期性激素的自然下降（雄激素直接减少以及由雄激素的外周芳构化产生的雌激素的低水平）与骨脆弱有关，但是这种效应在已接受雄激素剥夺治疗的雄性更明显。

在一些实施方案中，本发明的任意组合物包含任意形式的或本文所述的任意实施方案中的式 I 化合物。在一些实施方案中，本发明的任意组合物由任意形式的或在本文所述的任意实施方案中的式 I 化合物组成。在一些实施方案中，本发明的任意组合物主要由任意形式的或在本文所述的任意实施方案中的式I的化合物组成。在一些实施方案中，术语“包含”指包含所指的活性剂（例如式 I 的化合物）以及包含制药产业中已知的其它活性剂和药学上可接受的载体、赋形剂、润滑剂、稳定剂等。在一些实施方案中，术语“主要由...组成”指这样的组合物，其唯一的活性成分是所指的活性成分，但是，可以包括用于制剂的稳定、保存等的其它化合物，但是所述其它化合物不直接参与所指的活性成分的疗效。在一些实施方案中，术语“主要由...组成”可以指促进所述活性成分的释放的组分。在一些实施方案中，术语“由...组成”指含有所述活性成分和药学上可接受的载体或赋形剂的组合物。

在一个实施方案中，本发明提供联合制剂。在一个实施方案中，术语“联合制剂”特别地定义为“药盒(kit of parts)”，其意思是如以上定义的组合搭档可以独立地给药，或者通过使用具有不同量的组合搭档的不同的固定组合物给药，即同时地、并发地、分别地或依次地给药。那么，在一些实施方

案中，所述药盒的部件例如可以同时给药，或者按时间先后交替（即对于药盒任何部件在不同的时间点，以相同或不同的时间间隔）给药。在一些实施方案中，可以控制所述联合制剂中的组合搭档的总量的比率。在一个实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述组合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。

应该理解，本发明涉及用于任何适当的疾病、障碍或病症的本文所述的组合物和联合疗法，本领域的技术人员会意识到这一点。上文叙述了所述组合物和联合疗法对特定疾病、障碍和病症的某些应用，它们代表本发明的实施方案，而通过单独或作为所述联合疗法的部分来给药本文所述的化合物或使用本发明的组合物来治疗个体的所述疾病、障碍和病症的方法代表本发明其他的实施方案。

选择性雄激素调节剂化合物的生物活性

在一些实施方案中，本发明的化合物可以用于口服睾酮替代疗法。在其它实施方案中，适当取代的化合物用于：a) 男性避孕；b) 治疗各种激素相关的病症，例如与 ADAM 相关的病症，例如疲劳、抑郁、性欲降低、性功能障碍、勃起功能障碍、性腺功能减退症、骨质疏松症、脱发、肥胖症、少肌症、骨质减少、良性前列腺增生以及情绪和认知改变；c) 治疗与 ADIF 有关的病症，例如性功能障碍、性欲降低、性腺功能减退症、少肌症、骨质减少、骨质疏松症、认知和情绪变化、抑郁、贫血、脱发、肥胖症、子宫内膜异位症、乳腺癌、子宫癌和卵巢癌；d) 治疗和/或预防慢性肌萎缩；e) 治疗前列腺癌、前列腺癌成像、降低前列腺癌的发病率、使其中止或导致其消退；f) 治疗 I 型糖尿病；g) 治疗 II 型糖尿病；h) 压制或抑制糖尿病或降低其发病率；i) 治疗葡萄糖耐受不良；j) 治疗高胰岛素血症；k) 治疗胰岛素抵抗；l) 治疗糖尿病肾病；m) 治疗糖尿病神经病变；n) 治疗糖尿病视网膜病变；o) 治疗脂肪肝症；p) 治疗恶病质；q) 口服雄激素替代和/或其它临床治疗和/或诊断领域，包括本文所述的术语“治疗”所包括的任何实施方案。

在一些实施方案中，本发明的化合物在体内具有组织选择性雄激素活性和合成代谢活性，因此，可用于具体应用，本领域的技术人员会所意识

到这一点。

在一个实施方案中，本发明提供：a) 治疗罹患肌萎缩症的个体的方法；b) 治疗罹患营养不良的个体的方法；c) 治疗个体的骨相关病症的方法；d) 增加个体骨量的方法；e) 改善个体脂质分布的方法；f) 治疗动脉粥样硬化及其相关疾病的方法；g) 改善个体的灵活性和运动的方法；h) 治疗罹患侏儒症的个体的方法；i) 治疗罹患痛经的个体的方法；j) 治疗罹患精神性性交困难的个体的方法；k) 治疗罹患精子生成障碍性不育的个体的方法；这些方法包括向所述个体给药式 I 的化合物和/或所述化合物的类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、不纯物或晶体或它们的任意组合。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于各种应用和治疗其中需要改善认知、减少或治疗抑郁或其它神经保护作用的疾病。

在一个实施方案中，“认知”指认识的过程，特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中，“情绪”指脾气或精神状态。如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一个实施方案中，“抑郁”指涉及身体、情绪和思维的疾病，其影响人吃饭、睡觉的方式、自我感知的方式和考虑事物的方式。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩（social withdrawal）、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中，本发明的方法用于个体，其为人类。在另一个实施方案中，所述个体是哺乳动物。在另一个实施方案中，所述个体是动物。在另一个实施方案中，所述个体是无脊椎动物。在另一个实施方案中，所述个体是脊椎动物。

在一个实施方案中，所述个体是雄性。在另一个实施方案中，所述个体是雄性。在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述和所举例的，对于某些方法，雌性更有利地应答某些化合物的给药。

在一些实施方案中，尽管本文所述的方法可以用于治疗雄性和雌性，但是，如本文所述的，对于某些方法，雄性更有利地应答某些化合物的给药。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于以下各项的应用或治疗：脱发（hair loss）、脱发（alopecia）、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发或由应激诱导的脱发。在一个实施方案中，“脱发（hair loss）”或“脱发（alopecia）”指如极普遍类型的男人型脱发的脱发。脱发通常由头皮的斑块脱发开始，有时发展至全秃，甚至体毛脱落。脱发既影响男性也影响女性。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与罹患贫血的个体相关的疾病或病症的应用和治疗。在一个实施方案中，“贫血”指具有小于血液中红血细胞的正常数量或小于血液中血红蛋白的正常量、血细胞比容降低、或平均血细胞体积减小或血细胞尺寸减小的病症。在贫血时，血液的携氧能力下降。在一些实施方案中，治疗贫血在本文中也可以指治疗导致贫血的潜在因素，例如：a) 出血；b) 溶血（红血细胞过度破坏）；c) 红血细胞产生不足；和 d) 正常血红蛋白不足。在一些实施方案中，本发明的治疗贫血指治疗贫血的任何形式，包括再生障碍性贫血、苯中毒、范科尼贫血、新生儿溶血病、遗传性球形红细胞增多症、缺铁性贫血、骨质疏松症、恶性贫血、再生障碍性贫血、溶血性贫血、镰状细胞贫血、肾性贫血、地中海贫血、骨髓增生异常综合征和各种骨髓疾病。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与个体的性欲问题或个体的勃起功能障碍有关的疾病和/或病症的应用和/或治疗。在一个实施方案中，“性欲”可以指性本能。

在一个实施方案中，术语“勃起”指竖立或直立的能力。勃起组织是能够通过其含有的大量血管的膨胀而极大地膨胀并变硬的组织。

在本发明的另一个实施方案中，提供用于个体（即罹患雄激素依赖性病症的个体）的激素治疗的方法，所述方法包括使患者的雄激素受体与本发明的化合物和/或非类固醇激动剂和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合接触的步骤，上述化合物的量有效地使其与所述雄激素受体结合并实现改变雄激素依赖性病症。

在本发明的一个实施方案中，提供用于患者（即罹患雄激素依赖性病症的个体）激素替代治疗的方法，所述方法包括向个体给药足以实现改变所述个体的激素依赖性病症的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老、性腺功能减退症、少肌症、红细胞生成减少、骨质疏松症和与低雄激素（例如睾酮）或雌激素水平相关的任意的其它病症相关的病症。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症可以包括以雄激素或雌激素水平升高为特征的病症，包括多毛症、不育、多囊卵巢综合征、子宫内膜癌、乳腺癌、男人型脱发、前列腺癌、睾丸癌等，本领域的技术人员会知道这一点。对于这些病症，可以向所述个体单独地或联合其它治疗剂给药本文所述的化合物，本领域的技术人员会理解这一点。

在一个实施方案中，本发明提供治疗个体的癌症、降低其发病率、严重性或发病、延缓其进展、延长缓解期或延缓其发作的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌症是与雄性或雌性的生殖组织相关的激素依赖性或雄激素受体依赖性肿瘤（恶性或良性的），例如前列腺癌、卵巢癌、乳腺癌、子宫癌或睾丸癌等。

在一些实施方案中，本发明提供治疗个体癌前前兆或病变、降低其发病率的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。在一些实施方案中，这些癌前前兆是见于激素应答组织中的雄激素受体依赖性肿瘤或是与雄性或雌性的生殖组织例如前列腺、卵巢、乳腺、子宫或睾丸等相关。在一些实施方案中，这些癌前前兆包括例如前列腺、子宫颈等的任何局部的上皮内瘤样病变。在一些实施方案中，这种方法用于治疗在例如雄性或雌性生殖组织

的组织中的瘤或肿瘤前期、发育异常或增生。

在一个实施方案中，本发明提供化合物、组合物和/或它们在治疗良性前列腺增生(BPH)中的使用方法。“BPH（良性前列腺增生）”是前列腺的良性增大，它是在任何内脏器官中发现的最普通的良性增生性异常，并且是成年男性发病的主要病因。超过 75%的大于 50 岁的男性患 BPH，在九十岁的男性中，其患病率达到 88%。BPH 经常导致逐渐挤压穿过前列腺的尿道部分（前列腺尿道）。因为膀胱的不完全排空和尿急，这造成患者尿频急。尿流的梗阻也能导致一般的排尿失控，包括当希望排尿时排尿启动困难以及因为不能从膀胱排空尿而造成阻止尿流困难（一种称为充溢性尿失禁（overflow urinary incontinence）的病症，它可以导致尿路梗阻和泌尿衰竭（urinary failure））。

在本发明的一个实施方案中，治疗个体的良性前列腺增生(BPH)的方法包括向所述个体给药有效治疗所述个体的 BPH 的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、水合物、*N*-氧化物或它们的任意组合的步骤。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗个体的恶病质和/或与癌症有关的恶病质、减轻其严重性、降低其发病率或减少其发病的使用方法。在另一个实施方案中，所述癌症包括肾上腺皮质癌、直肠癌、膀胱癌、脑瘤、脑干胶质瘤、脑瘤、小脑星形细胞瘤、大脑星形细胞瘤（cerebral astrocytoma）、室管膜瘤、髓母细胞瘤、幕上原始神经外胚叶瘤（supratentorial primitive neuroectodermal）、松果体瘤、下丘脑胶质瘤、乳腺癌、类癌瘤、癌、子宫颈癌、结肠癌、结直肠癌、子宫内膜癌、食管癌、肝外胆管癌、尤文家族肿瘤（ewings family of tumors）(Pnet)、颅外胚细胞肿瘤、眼癌、眼内黑色素瘤、胆囊癌、胃癌、胚细胞瘤、性腺外肿瘤、妊娠滋养细胞肿瘤、头颈癌、下咽癌、胰岛细胞癌、喉癌、白血病、急性淋巴细胞性白血病、口腔癌、肝癌、肺癌、非小细胞肺癌、小细胞肺癌、AIDS 相关的淋巴瘤、中枢神经系统 （原发性）淋巴瘤、皮肤 T 细胞淋巴瘤、淋巴瘤（霍奇金病和非霍奇金病）、恶性间皮瘤、黑色素瘤、Merkel 细胞癌、转移性鳞癌、多发性骨髓瘤、浆细胞瘤、蕈样肉芽肿病、骨髓增生异常综合征、骨髓增殖性疾病、鼻咽癌、神经

母细胞瘤、口咽癌、骨肉瘤、卵巢上皮样癌、卵巢生殖细胞肿瘤、卵巢低恶性潜在肿瘤、胰腺外分泌癌（exocrine pancreatic cancer）、胰岛细胞癌、胰腺癌、鼻旁窦和鼻腔癌、甲状旁腺癌、阴茎癌、嗜铬细胞瘤癌、垂体癌、浆细胞瘤、前列腺癌、横纹肌肉瘤、直肠癌、肾细胞癌、涎腺癌、塞扎里综合征、皮肤癌、皮肤T细胞淋巴瘤、卡波西肉瘤、黑色素瘤、小肠癌、软组织肉瘤、软组织肉瘤、睾丸癌、恶性胸腺瘤、甲状腺癌、尿道癌、子宫癌、肉瘤、童年期异常癌、阴道癌、外阴癌、肾母细胞瘤或它们的任意组合。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗非小细胞肺癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗霍奇金病（或者在另一个实施方案中，非霍奇金病）、减轻其严重性、降低其发病率或延缓其发作的用途。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗结直肠癌、减轻其严重性、降低其发病率或延缓其发作的用途。

在一些实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗癌症、减轻其严重性、降低其发病率或减少其发病的用途。在另一个实施方案中，所述癌症包括雄激素AR依赖性肿瘤（恶性或良性的），例如前列腺癌、乳腺癌（男性或女性、可行手术或不能手术的）。在另一个实施方案中，所述SARM化合物是

ADT 的辅药（adjunct），所述 ADT 用于治疗前列腺癌、膀胱癌、脑癌、骨肿瘤、结肠癌、子宫内膜癌、肝癌、肺癌、淋巴癌、肾癌、骨肉瘤癌、卵巢癌、胰腺癌、阴茎癌、皮肤癌、甲状腺癌和/或激素依赖性癌。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 治疗骨相关的病症；b) 预防骨相关的病症；c) 压制骨相关的病症；d) 抑制骨相关的病症；e) 增加个体的骨强度；f) 增加个体的骨量；g) 抑制破骨细胞形成的用途。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：a) 加速骨修复；b) 治疗骨病症；c) 治疗骨密度降低；d) 治疗低骨矿物质密度(BMD)；e) 治疗骨量减少；f) 治疗代谢骨病；g) 促进骨生长或再生；h) 促进骨恢复；i) 促进骨折修复；j) 促进骨重建；k) 治疗成形外科（包括脸部、髋部或关节的）后的骨损害；l) 提高骨强度和功能；m) 增加骨皮质量；n) 增加小梁连接性。

在一个实施方案中，所述骨相关的病症是遗传性病症，在另一个实施方案中，是由特定疾病的治疗方案诱导的结果。例如，在一个实施方案中，本文所述的化合物用于治疗由癌症向骨转移而引起的骨相关的病症，或在另一个实施方案中，治疗例如由给予雄激素剥夺治疗应答个体的前列腺致癌作用而引起的骨相关的病症。

在一个实施方案中，所述骨相关的病症是骨质疏松症。在另一个实施方案中，所述骨相关的病症是骨质减少。在另一个实施方案中，所述骨相关的病症是骨吸收增加。在另一个实施方案中，所述骨相关的病症是骨折。在另一个实施方案中，所述骨相关的病症是骨脆弱。

在另一个实施方案中，所述骨相关的病症是骨矿物质密度(BMD)丢失。在另一个实施方案中，所述骨相关的病症是骨质疏松症、骨质减少、骨吸收增加、骨折、骨脆弱和 BMD 丢失的任意组合。每种病症代表本发明独立的实施方案。

在一个实施方案中，“骨质疏松”指由于钙和骨蛋白的消耗造成的骨变薄和骨量减少。在另一个实施方案中，骨质疏松症是全身性的骨骼疾病，其特

征是骨量低、骨组织退化，并由此导致骨脆弱和骨折易感性增加。在骨质疏松症患者，骨强度是异常的，在一个实施方案中，伴随由此引起的骨折风险增加。在另一个实施方案中，骨质疏松症使通常在见于骨中的钙和蛋白质胶原流失，在一个实施方案中，这导致骨性质异常或骨密度下降。在另一个实施方案中，受骨质疏松症影响的骨可仅仅由于通常不会造成骨折的轻微跌倒或损伤而骨折。在一个实施方案中，骨折可以是裂纹骨折的形式（如在髋骨折中）或压缩性骨折的形式（如在脊椎压迫性骨折中）。脊柱、髋和腕是骨质疏松诱发骨折的通常部位，但是，骨折也可以发生于其它骨骼部位。在另一个实施方案中，未加抑制的骨质疏松能够导致体位的改变、身体异常和灵活性下降。

在一个实施方案中，所述骨质疏松症由雄激素剥夺引起。在另一个实施方案中，所述骨质疏松症在雄激素剥夺后发生。在另一个实施方案中，所述骨质疏松症是原发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是继发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是绝经后骨质疏松症。在另一个实施方案中，所述骨质疏松症是幼年骨质疏松症。在另一个实施方案中，所述骨质疏松症是特发性骨质疏松症。在另一个实施方案中，所述骨质疏松症是老年性骨质疏松症。

在另一个实施方案中，所述原发性骨质疏松症是 I 型原发性骨质疏松症。在另一个实施方案中，所述原发性骨质疏松症是 II 型原发性骨质疏松症。每种类型的骨质疏松症代表本发明的独立的实施方案。

根据本发明的这一方面，在一个实施方案中，用本文所述的化合物或其组合治疗所述骨相关的病症。在另一个实施方案中，在给药本文所述的一种或多种化合物之前、同时或之后，可以提供给个体其它骨促进性化合物。在一个实施方案中，所述骨促进性化合物可以包括天然的或合成的物质。

在一个实施方案中，所述骨促进性化合物可以包括骨形态生成蛋白(BMP)；生长因子，例如表皮生长因子(EGF)、成纤维细胞生长因子(FGF)、转化生长因子(TGF)、胰岛素生长因子(IGF)、血小板源性生长因子(PDGF)；Hedgehog 蛋白（例如 *sonic* hedgehog、*indian* hedgehog 和 *desert* hedgehog）；激素，例如促卵泡激素、甲状旁腺素、甲状旁腺激素相关肽、激活素、抑制素、滤泡抑素、*frizzled* 蛋白、*frzb* 蛋白或 *frazzled* 蛋白；BMP 结合蛋白，例

如脊索蛋白和胎球蛋白；细胞因子，例如 IL-3、IL-7、GM-CSF；趋化因子，例如嗜酸细胞活化趋化因子；胶原；骨钙蛋白；骨黏连蛋白等；本领域的技术人员会理解这一点。

在另一个实施方案中，本发明用于治疗骨病的组合物可以包含本文所述的一种或多种化合物、额外的一种或多种骨促进性化合物和骨原细胞。在一个实施方案中，骨原细胞可以是可以被诱导分化为成骨细胞的干细胞或祖细胞。在另一个实施方案中，所述细胞可以是成骨细胞。在另一个实施方案中，可以向个体给药编码骨促进性化合物的核酸，这应该被认为是本发明的部分。

在一个实施方案中，本发明的方法包括含给药用于治疗骨质疏松症的化合物。在另一个实施方案中，本发明的方法包括给药化合物（与 SERM 联合），用于治疗骨质疏松症。在另一个实施方案中，所述 SERM 是三苯氧胺、4-羟三苯氧胺、艾多昔芬、托瑞米芬、奥培米芬、屈洛昔酚、雷诺昔芬、阿佐昔芬、巴多昔芬、PPT (1,3,5-三(4-羟基苯基)-4-丙基-1*H*-吡唑)、DPN (二芳基丙腈)、拉索昔芬、哌喷昔芬、EM-800、EM-652、萘福昔定、秦唑昔芬、替米利芬、磷酸米泼昔芬、RU 58,688、EM 139、ICI 164,384、ICI 182,780、氯米芬、MER-25、二乙基己烯雌酚、香豆雌酚、染料木黄酮、GW5638、LY353581、珠氯米芬、恩氯米芬、地马孕酮醋酸盐、DPPE、(*N,N*-二乙基-2- {4-(苯基甲基)- 苯氧基} 乙胺)、TSE-424、WAY-070、WAY-292、WAY-818、cyclocommunol、普林贝瑞、ERB-041、WAY-397、WAY-244 ERB-196、WAY-169122、MF-101、ERb-002、ERB-037、ERB-017、BE-1060、BE-380、BE-381、WAY-358、[18F] FEDNP、LSN-500307、AA-102、半枝莲、CT-101、CT-102、VG-101。

在另一个实施方案中，本发明的方法包括与二膦酸盐联合给药所述 SARM 化合物用于治疗骨质疏松症，所述二膦酸盐例如阿屈膦酸盐、替鲁膦酸（tiludroate）、氯屈膦酸钠（clodroniate）、帕米磷酸钠、羟乙膦酸盐、阿屈膦酸盐、唑屈膦酸盐（zolendronate）、英卡膦酸二钠（cimadronate）、奈立膦酸钠（neridronate）、米诺膦酸（minodronic acid）、依班膦酸盐、利塞膦酸盐或 homoresidronate。

在另一个实施方案中，本发明的方法包括与降钙素例如鲑精组蛋白

（salmon）、依降钙素、SUN-8577 或 TJN-135 联合给药所述化合物用于治疗骨质疏松症。

在另一个实施方案中，本发明的治疗骨质疏松症的方法包括联合以下物质给药所述 SARM 化合物：a) 维生素 D 或衍生物，例如 ZK-156979；b) 维生素 D 受体配体和类似物，例如骨化三醇、钙三醇(topitriol)、ZK-150123、TEI-9647、BXL-628、Ro-26-9228、BAL-2299、Ro-65-2299 或 DP-035；c) 雌激素、雌激素衍生物或结合型雌激素；d) 抗雌激素药、孕激素或合成雌激素/孕激素；e) RANK 配体单克隆抗体，例如 denosumab(以前称为 AMG162 (Amgen))；f) αvβ3 整合素受体拮抗剂；g) 破骨细胞空泡型 ATP 酶抑制剂；h) 结合 VEGF 的破骨细胞受体拮抗剂；i) 钙受体拮抗剂；j) PTh（甲状旁腺素）和类似物、PTHrP 类似物（甲状旁腺素相关肽）；k) 组织蛋白酶 K 抑制剂（AAE581 等）；l) 雷尼酸锶；m) 替勃龙；n) HCT-1026、PSK3471；o) 麦芽糖镓（gallium maltolate）；p) Nutropin AQ；q) 前列腺素（用于骨）；r) p38 蛋白激酶抑制剂；s) 骨形态生成蛋白；t) BMP 拮抗抑制剂；u) HMG-CoA 还原酶抑制剂；v) 维生素 K 或衍生物；w) 依普黄铜；x) 氟化盐；y 饮食钙补充剂和 z) 骨保护素。

在一个实施方案中，本发明的方法用于治疗由激素紊乱、破坏或不平衡引起的或与之相关的疾病或病症。在一个实施方案中，所述激素紊乱、破坏或不平衡包括激素过量。在另一个实施方案中，所述激素紊乱、破坏或不平衡包括激素缺乏。在一个实施方案中，所述激素是类固醇激素。在另一个实施方案中，所述激素是雌激素。在另一个实施方案中，所述激素是雄激素。在另一个实施方案中，所述激素是糖皮质激素。在另一个实施方案中，所述激素是皮质类固醇。在另一个实施方案中，所述激素是黄体生成素（LH）。在另一个实施方案中，所述激素是促卵泡激素（FSH）。在另一个实施方案中，所述激素是本领域已知的任何其它激素。在另一个实施方案中，所述激素紊乱、破坏或不平衡与绝经有关。在另一个实施方案中，所述激素紊乱、破坏或不平衡与男性更年期、男性更年期血管舒缩综合征、男性更年期乳腺发育、肌肉强度和/或功能下降、骨强度和/或功能下降和发怒有关。在另一个实施方案中，激素缺乏是特定处理的结果，如治疗个体疾病或病症的副产物。例如，所述激素缺乏可以是作为个体前列腺癌疗法的雄激素消耗的结果。

每种可能性代表本发明的独立的实施方案。

在另一个实施方案中，本发明涉及治疗少肌症或恶病质和与其相关的病症（例如骨疾病或病症）。

在一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合的以下用途：1) 治疗肌萎缩症；2)预防肌萎缩症；3) 治疗、预防、压制、抑制或减少归因于肌萎缩症引起的肌肉损失；4) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌萎缩；和/或 5) 治疗、预防、抑制、减少或压制归因于肌萎缩症的肌肉蛋白分解代谢；和/或治疗、预防、抑制、减少或压制归因于终末期肾脏疾病或 CKD 的肌萎缩；和/或 6) 治疗、预防、抑制、减少或压制脆弱。

在另一个实施方案中，用于治疗罹患肌萎缩症或本文所述的任何病症的个体的化合物的用途包括给药包含本文所述的化合物的药物组合物。在另一个实施方案中，所述给药步骤包括将液体形式的所述药物组合物经静脉内、动脉内或肌内注射给所述个体；在所述个体体内皮下埋植含有所述药物组合物的小丸；口服向所述个体给药液体或固体形式的所述药物组合物；或向所述个体的皮肤表面局部施用所述药物组合物。

肌肉是主要用作动力源的身体组织。身体的肌肉有三种类型：a) 骨骼肌——负责身体的四肢和外部区域运动的肌肉；b) 心肌——心脏肌肉；和 c) 平滑肌——位于动脉和肠壁中的肌肉。

在本文中，消耗性（wasting）病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症或感染的结果而发生，或可归因于生理或代谢状态，例如因长期卧床休息或当肢体被固定（例如在铸型中）时发生的废用性失调。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，如本文交替使用的，“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一

个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍的结果而发生。在一个实施方案中，所述病状、疾患、疾病或病症是慢性的。在另一个实施方案中，所述病状、疾患、疾病或病症是遗传性的。在另一个实施方案中，所述病状、疾患、疾病或病症是神经的。在另一个实施方案中，所述病状、疾患、疾病或病症是感染性的。如本文所述的，为之给药本发明的化合物和组合物的病状、疾病、病症或障碍是直接或间接产生肌肉量的消耗（即损失），即肌萎缩症的疾病。

在一个实施方案中，个体的肌萎缩由所述个体的肌营养不良症、肌萎缩、伴 X 染色体的脊延髓肌萎缩症（SBMA）引起。

所述肌营养不良症是遗传性疾病，其特征是控制运动的骨骼肌或随意肌的进行性衰减和退化。心脏肌肉和一些其它不随意肌也受到某些形式的肌营养不良的影响。肌营养不良（MD）的主要形式是：迪谢内肌肉营养不良、强直性肌营养不良、迪谢内肌肉营养不良、贝克肌营养不良、肢肌营养不良、面肩胛臂肌营养不良、先天性营养不良症、眼咽肌营养不良、远侧肌营养不良和埃-德二氏肌营养不良。

肌营养不良症可以影响所有年龄的人群。尽管某些形式首先在婴儿或儿童中出现，其它可能直到中年或更晚才出现。迪谢内 MD 是最普通的形式，一般影响儿童。强直性肌营养不良是这些疾病中在成人中的最通常的疾病。

肌萎缩（MA）以肌肉的消耗或减少和肌肉量的减少为特征。例如，小儿麻痹症后期 MA 是作为小儿麻痹小儿麻痹症后期综合征（PPS）的一部分而发生的肌肉萎缩。所述萎缩包括虚弱、肌疲劳和疼痛。

其它类型的MA是伴X染色体的脊延髓肌萎缩症(SBMA,也称为Kennedy病)。该病由X染色体上的雄激素受体基因的缺陷引起,仅影响男性,其在成年期发作。因为主要病因是雄激素受体突变,所以雄激素替代不是流行的治疗策略。有一些调查研究,其中给予外源性丙酸睾酮以提高雄激素的水平,这有希望克服雄激素不敏感性并可能提供合成代谢效应。然而,使用超生理水平的睾酮用于补充会有局限性和其它潜在的严重并发症。

少肌症是折磨老人和慢性病患者的使人衰弱的疾病,其特征是肌肉量和功能的损失。而且,瘦体重的增加与某些肌萎缩症的发病率和死亡率降低有关。而且,其它情况和病症也与肌萎缩症有联系并能导致肌萎缩。例如,有研究显示,在慢性下腰痛的严重病例中,出现椎旁肌萎缩。

肌萎缩和其它组织消耗也与高龄有关。相信,在老年人中,全身虚弱归因于肌萎缩。随着身体的老化,更多比例的骨骼肌被纤维组织代替。结果,肌肉的力量、性能和耐力显著下降。

由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌肉萎缩或其它组织消耗。研究显示,在长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中,出现长期单侧肌萎缩和体重减少。

中枢神经系统(CNS)损伤或损害也与肌肉萎缩和其它消耗性病症有关。CNS损伤或损害可由例如疾病、创伤或化学药品引起。其例子有中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。在一个实施方案中,CNS损害或损伤包括阿尔茨海默氏病(AD)、发怒(情绪)、厌食症、神经性厌食症、与衰老有关的厌食症和/或自信(情绪)。

在另一个实施方案中,肌萎缩和其它组织消耗可能由酒精中毒引起,可以用本发明的化合物和组合物来治疗,这代表它们的实施方案。

在一个实施方案中,本发明提供本文所述的化合物或其类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合用于治疗个体的消耗性疾病、障碍或病症的用途。

在一个实施方案中,所述被治疗的消耗性疾病、障碍或病症与慢性病有关。

在一些实施方案中,本发明涉及治疗可能在肌萎缩、体重减少、营养不

良、饥饿中表现出的任何消耗性病症、或任何归因于组织量减少的功能消耗或缺失。

在一些实施方案中，消耗性疾病或病症，例如恶病质、营养不良、结核病、麻风病、糖尿病、肾脏病、慢性障碍性肺病（COPD）、癌症、终末期肾衰竭、少肌症、肺气肿、骨软化症或心肌病，可以通过本发明的方法，经给药本文所述的 SARM 化合物、包含它的组合物、附加或不附加为所治疗的病症提供疗效的药物、化合物或药剂来治疗。

在一些实施方案中，消耗是由于感染肠道病毒、Epstein-Barr 病毒、带状疱疹、HIV、锥虫、流感（influenze）、柯萨奇病毒、立克次氏体、旋毛虫、血吸虫或分枝杆菌，在一些实施方案中，本发明提供其治疗方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。心原性恶病质，即心肌和骨骼肌的肌肉蛋白消耗，是充血性心力衰竭的特征。癌症恶病质是发生在患有实体瘤和恶性血液病的患者的综合征，其表现为因脂肪组织和瘦肌肉量的大量消耗而导致的体重减少。

恶病质也见于获得性免疫缺陷综合征（AIDS），人类免疫缺陷病毒（HIV）相关肌病和/或肌无力/肌萎缩是 AIDS 比较通变的临床表现。患有 HIV 相关肌病或肌无力/肌萎缩的个体通常经受严重的体重下降、全身的或近端的肌无力、压痛和肌萎缩。

在一些实施方案中，本发明提供用于治疗个体感染、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药包含化合物和免疫调节剂、抗感染剂、基因治疗剂或它们的组合的组合物免疫调节剂。在一个实施方案中，所述抗感染剂可以是抗真菌剂、抗细菌剂、抗病毒剂、或抗寄生虫剂或它们的组合。在一些实施方案中，感染包括放射菌病、边虫病、炭疽、曲霉病、菌血症、细菌真菌病、巴尔通体感染、肉毒中毒、布氏菌病、伯霍尔德杆菌感染、弯曲杆菌传染、念珠菌病、猫抓病、衣原体传染、霍乱、梭菌感染、球孢子菌病、交叉感染、隐球菌病、皮肤真菌病、白喉病、埃里希体病、大肠杆菌感染、坏死性筋膜炎、梭杆菌感染、气性坏疽、革兰氏阴性细菌感染、革兰氏阳性细菌感染、组织胞浆菌病、脓疱病、克雷伯菌感染、军团杆菌病、麻风病、钩端螺旋体病、利斯特菌感染、莱姆病、马杜拉分支菌病、类鼻疽、分枝杆

菌感染、支原体感染、真菌病、诺卡尔菌感染、甲癣、瘟疫、肺炎球菌感染、假单胞菌感染、鹦鹉热、Q热、鼠咬热、回归热、风湿热、立克次体感染、洛基山斑点热、沙门菌感染、猩红热、恙虫热斑疹伤寒、败血症、性传播疾病、葡萄球菌感染、链球菌感染、破伤风、蜱传播性疾病(tick-borne diseases)、结核病、土拉菌病、伤寒、虱传斑疹伤寒、弧菌感染、雅司病、耶尔森菌感染、人兽互通病、接合菌病、获得性免疫缺陷综合征、腺病毒科感染、甲病毒感染、虫媒病毒传染、Borna 病、布尼亚病毒科感染、嵌杯病毒科感染、水痘、冠状病毒科感染、柯萨奇病毒感染、巨细胞病毒感染、登革热、DNA病毒感染、触染性痘疮、脑炎、虫媒病毒、Epstein-barr 病毒感染、传染性红斑、汉坦病毒感染、出血热、病毒性肝炎、病毒性人单纯疱疹、带状疱疹、耳部带状疱疹、疱疹病毒科感染、传染性单核细胞增多症、人拉沙热、麻疹、传染性软疣、流行性腮腺炎、副粘病毒科感染、白蛉热、多瘤病毒感染、狂犬病、呼吸合胞体病毒感染、裂谷热、RNA 病毒感染、风疹、慢病毒疾病、天花、亚急性硬化性全脑炎、肿瘤病毒感染、疣、西尼罗热、病毒性疾病、黄热病、阿米巴病、异尖线虫病、蛔虫病、巴贝虫病、人芽囊原虫感染、臭虫叮咬、绦虫感染、美洲锥虫病、隐孢子虫病、环孢子虫感染、囊虫病、双核阿米巴病、裂头绦虫病、龙线虫病、包虫病、体外寄生虫感染、丝虫病、贾第虫病、蠕虫病、钩虫感染、幼虫移行症、利什曼病、虱寄生、罗阿丝虫病、疟疾、感染、蝇蛆病、盘尾丝虫病、原虫感染、疥疮、血吸虫病、(寄生虫性)皮肤病、类圆线虫病、绦虫病、弓蛔虫病、弓形体病、旋毛虫病、滴虫感染、锥虫病、非洲锥虫病或者鞭虫感染。

在一些实施方案中，本发明提供用于治疗个体肌骨疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药或它们的组合。在一些实施方案中，肌骨疾病包括软骨发育不全、获得性骨肥大综合征、尖头并指（趾）畸形、关节炎、关节挛缩、关节病、神经原性滑囊炎、软骨疾病、锁骨颅骨发育不良、畸形足、筋膜间隔综合征、颅面骨发育不全、颅缝早闭、皮肌炎、杜普伊特伦氏挛缩、侏儒症、埃-范二氏综合征、内生软骨瘤病、酸

细胞增多性肌痛综合征、外生骨疣、筋膜炎、疲劳综合征、纤维肌痛、骨纤维性结构不良、多骨纤维性结构不良、扁平足、足畸形、弗莱尔伯格二蹠骨远端缺血坏死、漏斗胸、Goldenhar 综合征、痛风、拇外翻、髋脱位、骨肥厚、椎间盘移位、歌舞伎化妆综合征(kabuki make-up syndrome)、克-费二氏综合征、兰-吉综合征、莱-佩二氏病、脊柱前凸、下颌骨颜面发育不全、肢骨纹状肥大、线粒体肌病、肌痛性痉挛、肌痉挛状态、肌营养不良、肌肉骨骼畸形、肌骨疾病、肌炎、骨化性肌炎、肌管性肌病、畸形性骨炎、骨性关节炎、骨软骨炎、成骨不全、骨髓炎、骨坏死、骨硬化症、骨质疏松症、波伦综合征、复发性多软骨炎、风湿性多肌痛、多肌炎、横纹肌溶解、风湿性疾病、鲁-辛二氏综合征、绍伊尔曼氏病、脊柱侧凸、塞佛氏病/跟骨骨突炎、脊柱疾病、脊髓骨赘病、椎管狭窄、强直性脊柱炎、脊椎前移、施普伦格耳畸形、滑膜炎、肌腱病变、网球肘、腱鞘炎、致死性发育不全或 Tietze 综合征。

在一些实施方案中，本发明提供用于治疗个体的消化系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗胃肠系统的药、抗感染药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，胃肠疾病包括腺瘤结肠息肉、Alagille综合征、肛门疾病、阑尾炎、巴雷特食管、胆道闭锁、胆道疾病、卡罗利病、乳糜泻、胆管炎、胆囊炎、胆石症、溃疡性结肠炎、克罗恩病、吞咽障碍、十二指肠的溃疡、痢疾、假膜性小肠结肠炎、食管失弛症、食管闭锁、食管炎、胰腺外分泌功能不全、脂肪肝、大便失禁、胃炎、肥厚性胃炎、胃肠炎、胃食管反流、胃肌轻瘫、痔疮、肝静脉血栓形成、肝炎、慢性肝炎、膈疝、食管裂孔疝、希尔施普龙病、高血压(HTN)、门静脉高压、炎性肠疾病、肠疾病、肠肿瘤、肠神经元发育异常、肠梗阻、肠易激综合征、乳糖不耐受、肝硬化、肝病、梅克尔憩室、胰腺疾病、胰腺肿瘤、胰腺炎、消化性溃疡、杰格斯综合征、直肠炎、直肠疾病、直肠脱垂、短肠综合征、气管食管瘘、惠普尔病或卓林格-艾丽逊综合征。

在一些实施方案中，本发明提供用于治疗个体口颚病、降低其发病率、

延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，口颚病包括舌系带过短、夜磨牙症、口灼伤综合征、唇炎、巨颌症、唇裂、含牙囊肿、龈炎、良性迁移性舌炎、唇疱疹、路德维希咽峡炎、巨舌、迈-罗二氏综合征、牙周疾病、皮埃尔·罗班综合征、下颌前突、涎腺疾病、流涎、口疮性口炎、颞下颌关节障碍、颞下颌关节功能紊乱综合征或者口干燥症。

在一些实施方案中，本发明提供用于治疗个体的呼吸道疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗中枢神经系统的药、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，呼吸道疾病包括气道阻塞、呼吸暂停、石棉沉着病、哮喘、哮喘诱导的肌无力或者骨虚弱、肺膨胀不全、铍中毒、支气管疾病、支气管扩张、细支气管炎、闭塞性细支气管炎机化性肺炎、支气管炎、支气管肺发育不良、慢性阻塞性肺病(COPD)、感冒、咳嗽、胸腔积脓、会厌炎、糖皮质激素(GC)引起的肌病或骨质减少、咯血、肺动脉高压、通气过度、卡塔格内综合征、肺脓肿、肺病、胎便吸入综合征、胸腔积液、胸膜炎、肺炎、气胸、肺泡蛋白质沉着症、慢性阻塞性肺病、肺水肿、肺栓塞、肺气肿、肺纤维化、呼吸窘迫综合征、新生儿呼吸过敏症、呼吸道感染、鼻硬结病、弯刀综合征、严重急性呼吸器官综合病、矽肺、睡眠呼吸暂停、中央喘鸣、气管狭窄、归因于哮喘的肌肉量或骨量减少、慢性阻塞性肺病(COPD)中的消耗、韦格纳氏肉芽肿或者百日咳。

在一些实施方案中，本发明提供用于治疗个体耳鼻喉疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，耳鼻喉疾病包括中耳胆脂瘤、哮吼、耳聋、鼻出血、听力损失、听觉过敏、迷路炎、喉炎、喉

软化、喉狭窄、乳突炎、梅尼埃病、鼻塞、鼻息肉、耳炎、耳鼻喉病、耳硬化、咽炎、老年性耳聋、咽后脓肿、鼻炎、鼻窦炎、耳鸣、扁桃体炎、鼓膜穿孔、前庭神经元炎、声带麻痹或者语音障碍。

在一些实施方案中，本发明提供用于治疗个体神经系统疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗中枢神经系统的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，神经系统疾病包括自主神经系统疾病、中枢神经系统疾病、颅神经疾病、脱髓鞘疾病、神经系统畸形、神经病学表现或神经肌肉疾病。

在一些实施方案中，自主神经系统疾病包括灼性神经痛或反射性交感神经营养障碍。

在一些实施方案中，中枢神经系统疾病包括阿尔茨海默氏病、蛛网膜炎、脑脓肿、脑缺血、中枢神经系统感染、大脑性瘫痪、脑血管障碍、皮质基底节变性(corticobasal ganglionic degeneration, CBGD)、Creutzfeldt-Jakob 综合征、丹-沃二氏综合征、痴呆、脑炎、脑脊髓炎、癫痫症、癫痫症诱导的性腺机能减退和/或代谢增进状态、特发性震颤、弗里德赖希共济失调、杰茨曼-斯脱司勒-史茵克病、哈-斯二氏综合征、亨廷顿病、脑积水、缺氧、失眠、脑缺血发作（ischemic attack）、库鲁病、Landau-Kleffner 综合征、Lewy 体病、马-约病、Meige 综合征、脑膜炎、细菌性脑膜炎、病毒性脑膜炎、偏头痛、运动障碍、多系统萎缩、脊髓炎、橄榄体脑桥小脑萎缩、帕金森病、帕金森障碍、脊髓灰质炎、脊髓灰质炎后综合征、朊病毒病、假脑瘤、希-德二氏综合征、婴儿痉挛、脊髓疾病、核上性麻痹、脊髓空洞症、丘脑疾病、抽搐性运动障碍、多动秽语综合征或葡萄膜脑膜脑炎综合征。在一些实施方案中，所述中枢神经系统疾病是囊性纤维化病诱导的性腺机能减退状态。

在一些实施方案中，颅神经疾病包括 Bell 麻痹、颅神经疾病、面部半侧萎缩、面神经痛、舌咽神经疾病、莫比乌斯综合征或者三叉神经痛。

在一些实施方案中，中枢神经系统疾病包括对中枢神经系统（CNS）的损伤或损害。在一些实施方案中，对 CNS 的损伤或损害可能与肌萎缩症有关。

对 CNS 的损伤或损害可以由例如疾病、创伤或化学试剂引起。其例子是中枢神经损伤或损害、周围神经损伤或损害和脊髓损伤或损害。

涉及脊髓损伤（SCI）患者的研究已经显示，在 SCI 后，中枢神经递质可能会改变，造成下丘脑-垂体-肾上腺轴功能障碍，它的破坏导致睾酮和其它激素水平的严重下降。SCI 或其它急性疾病或创伤特征性地包括分解代谢增强和合成代谢活动减低，导致易于损失瘦身体组织的病症，并经常伴随紊乱的营养利用。瘦体重的损失的影响包括伤口扩展和愈合机制受损，使问题进一步复杂化。由于营养不良和蛋白分解代谢加上固定，脊髓损伤的患者处于高度的患褥疮的风险中。

在一个实施方案中，本发明的方法可以治疗各种 CNS 损伤。在一个实施方案中，CNS 损伤可以指神经细胞膜的分解，或者在另一个实施方案中，指神经不能产生或传播神经冲动，或者在另一个实施方案中，指神经细胞的死亡。损伤包括直接或间接影响 CNS 的正常功机能的损害。所述损伤可能是结构性、物理性或机械性损伤，并可能在挤压、压缩或拉伸神经纤维的情况下由身体冲击造成。或者，所述细胞膜可能因疾病、化合失调或生理功能障碍，例如缺氧（例如卒中）、动脉瘤或再灌注而被破坏或降解。CNS 损伤非限制性地包括例如对视网膜神经节细胞损害、外伤性脑损伤、卒中相关的损伤、脑动脉瘤相关的损伤、脊髓损伤（包括单瘫、双侧瘫痪、截瘫、偏瘫和四肢瘫痪）、神经增殖性病症或神经性疼痛综合征。

由于对哺乳动物脊髓的损伤，脊髓中神经之间的连接断裂。这种损伤阻断受该损伤影响的神经束的神经冲动的流动，结果损害感觉功能和运动功能。对脊髓的损伤可能缘于脊髓的压缩或其它挫伤、脊髓挤压或切断。脊髓切断（本文中也称为“横切”），可能是脊髓的完全切断或可能是不完全切断。

在一些实施方案中，治疗罹患 CNS 损伤（或在另一个实施方案中为罹患脊髓损伤）的个体的方法可能伴随用损伤部位的电刺激和给药嘌呤核苷或其类似物（例如美国专利申请公开 20040214790A1 中所述）治疗所述个体。

在一些实施方案中，脱髓鞘疾病包括肾上腺脑白质营养不良、亚历山大病、卡纳万病、脱髓鞘病、Schilder 弥漫性脑硬化、球形细胞脑白质营养不良、异染性脑白质营养不良、多发性硬化或视神经脊髓炎。

在一些实施方案中，神经系统畸形包括阿-蔡二氏畸形、夏-马-图三氏病、

脑膨出、遗传性运动和感觉性神经病、透明隔-视神经发育不良、隐性脊柱裂或椎管闭合不全。

在一些实施方案中，神经病学表现包括失认症、遗忘症、命名不能症、失语症、失用症、背痛、布朗-塞卡尔综合征、小脑性共济失调、舞蹈症、交流障碍、意识错乱、头晕、诵读困难、张力失常、面神经麻痹、肌束震颤、步态障碍、神经性头痛、偏瘫、记忆障碍、智力低下、缄默症、肌阵挛、颈痛、非语言学习障碍、嗅觉障碍、疼痛、麻痹、幻肢、面容失认症、四肢瘫痪、癫痫发作、痉挛、言语障碍、共同感觉迟发性运动障碍、味觉障碍、斜颈、震颤、牙关紧闭、意识丧失或眩晕。

在一些实施方案中，神经肌肉疾病包括肌萎缩侧索硬化、臂丛神经炎、臂丛神经病、延髓性麻痹、腕管综合征、肘管综合征、糖尿病神经病变、家族性自主神经异常、格-巴二氏综合征、遗传性感觉和自主神经系统神经病、米勒·费希尔综合征、运动神经元病、脊髓性肌萎缩、重症肌无力、先天性结构性肌病、神经卡压综合征、神经痛、神经肌肉疾病、家族周期性麻痹、周围神经系统疾病、POEMS 综合征、多神经病、多发性神经根病、雷夫叙姆病、坐骨神经痛、儿童脊髓性肌萎缩、僵人综合征（stiff-person syndrome）、胸廓出口综合征或尺神经压缩综合征。

在一个实施方案中，治疗罹患神经系统疾病的个体的方法包括治疗所述个体的任何继发性病症，所述病症由所述个体患有神经系统疾病而引起，其中的一些在本文中有叙述。

在一些实施方案中，本发明提供用于治疗个体的眼睛疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、治疗心血管系统的药、抗感染药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，眼睛疾病包括急性区域性隐匿性外层视网膜病变(acute zonal occult outer retinopathy)、埃迪综合征、白化病、眼睛黑蒙（ocular-amaurosis）、弱视（fugax）、弱视（amblyopia）、无虹膜、瞳孔不等、无眼畸形、无晶状体、散光、睑缘炎、眼睑下垂、睑痉挛、盲、白内障、睑板腺囊肿、脉络膜视网膜炎、无脉络膜、眼缺损、色觉缺陷、结膜炎、角膜疾病、角膜营养不良、角膜水肿、

角膜溃疡、糖尿病视网膜病变、复视、双行睫、干眼综合征、Duane 眼球后退综合征、睑外翻、睑内翻、内斜视、虹膜色素剥脱综合征、外斜视、眼出血、眼睛瘤、眼睑疾病、悬浮物、广泛纤维化综合征(general fibrosis syndrome)、青光眼、环状萎缩、偏盲、血小板病-白化病综合征、睑腺炎、霍纳综合征、远视、前房出血、虹膜炎、Kearns-Sayer 综合征、角膜炎、圆锥角膜、泪器疾病、泪管阻塞、晶体疾病、黄斑变性、小眼、近视、病理性眼震、Kearns-Sayer、动眼神经疾病、眼肌麻痹、视神经萎缩、视神经疾病、视神经炎、视神经病变、眶蜂窝织炎、视神经乳头水肿、Peter 异常、老视、翼状胬肉、瞳孔失调、屈光不正、视网膜脱离、视网膜疾病、视网膜静脉闭塞、视网膜色素变性、早产儿视网膜病、视网膜劈裂症、巩膜炎、暗点、斜视、Thygeson 表层点状角膜炎、沙眼、葡萄膜炎、白点综合征、视觉障碍或者玻璃体病症。

在一些实施方案中，本发明提供治疗个体的泌尿道和/或男性生殖器疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿系疾病和/或男性生殖器疾病包括抗肾小球基底膜疾病、阴茎头炎、膀胱外翻、膀胱肿瘤、隐睾症、间质性膀胱炎、肾性尿崩症、附睾炎、富尼埃坏疽、肾小球肾炎、古德帕斯丘综合征、血性精液、血尿、溶血尿毒症综合征、肾盂积水、尿道下裂、阳痿、不育、肾结石、急性肾功能衰竭、慢性肾功能衰竭、急性肾小管坏死、海绵肾、多囊性肾发育不良、遗传性肾炎、肾病、肾病综合征、夜尿、少尿、阴茎疾病、阴茎硬结、阴茎肿瘤、包茎、阴茎异常勃起、前列腺疾病、良性前列腺增生、前列腺肿瘤、蛋白尿、肾盂肾炎、赖特病、肾动脉梗阻、精索扭转、睾丸疾病、尿道狭窄、尿道炎、尿潴留、泌尿道感染、排尿障碍、泌尿道和男性生殖器疾病、泌尿系疾病、精索静脉曲张、膀胱或尿道回流。

在一些实施方案中，本发明提供治疗个体的皮肤病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含化合物和抗癌药、免疫

调节剂、治疗皮肤病症的药、抗感染药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，皮肤病症包括痤疮、光线性角化病、脱发、雄激素性脱发、斑秃、继发化学疗法的脱发、继发放射疗法的脱发、由瘢痕形成诱导的脱发、应激诱导的脱发、血管瘤、足癣、水源性瘙痒症、特应性皮炎、脱发、早年脱发、男人性脱发、雄激素性脱发、基底细胞癌、烧伤、褥疮、白塞氏病、睑缘炎、疖、Bowen 病、大疱性类天疱疮、复发性口溃疡、痈、组织蜂窝炎、氯痤疮、手脚慢性皮炎、出汗不良症、感冒疮、接触性皮炎、匍行疹、头皮屑、皮炎、疱疹样皮炎、皮肤纤维瘤、尿布疹、湿疹、大疱性表皮松解症、丹毒、红皮病、擦伤水泡、生殖器疣、化脓性汗腺炎、荨麻疹、多汗症、鱼鳞病、脓疱病、边缘性皮霉病、卡波西肉瘤、瘢痕疙瘩、角化棘皮瘤、毛发角化病、虱感染、扁平苔癣、慢性单纯性苔癣、脂肪瘤、淋巴结炎、恶性黑色素瘤、黑斑病、痱、传染性软疣、钱币状皮炎、佩吉特乳头病、虱病、天疱疮、口周皮炎、光变态反应、光过敏、玫瑰糠疹、毛发红糠疹、银屑病、雷诺病、钱癣（ring worm）、酒渣鼻、疥疮、硬皮病、皮脂腺囊肿、脂溢性角化症、脂溢性皮炎、带状疱疹、皮肤癌、皮赘、蜘蛛状血管病、鳞状细胞癌、淤滞性皮炎、蜱叮咬、须癣、头癣、体癣、股癣、脚癣、甲癣、花斑癣、癣、潜蚤病、癜风病或疣。

在一个实施方案中，所述皮肤病症是伤口或烧伤。在一些实施方案中，发现伤口和/或溃疡从皮肤突出或在粘膜表面上或是器官梗死形成的结果。伤口可能是软组织缺损或损害或者潜在疾病的结果。在一个实施方案中，术语“伤口”指具有正常的组织结构完整性的破坏的身体损伤。该术语也包括术语“疮”、“损害”、“坏死”和“溃疡”。在一个实施方案中，术语“疮”指皮肤或粘膜的任何损害，术语“溃疡”指器官或组织表面的局部缺损或陷凹，其由坏死组织的腐离产生。损害一般与任意的组织缺损有关。坏死与由感染、损伤、发炎或梗死形成引起的死亡组织有关。所有这些都由术语“伤口”包括，所述“伤口”指愈合过程中的任意特定阶段的任何伤口，所述阶段包括任何愈合开始前的阶段，或甚至在产生特定伤口（像外科切口）（预防治疗）之前的阶段。

待根据本发明预防和/或治疗的伤口的例子是，例如无菌伤口、挫伤、切伤、撕裂伤、非穿透伤（即其中无皮肤破坏但损伤下面的结构的伤口）、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口、皮下创伤等。疮的例子有

褥疮、口疮、铬毒性溃疡、感冒疮、受压溃疡等。溃疡的例子是消化性溃疡、十二指肠溃疡、胃溃疡、痛风性溃疡、糖尿病性溃疡、高血压缺血性溃疡、淤积性溃疡、小腿溃疡 (静脉溃疡)、舌下溃疡、粘膜下溃疡、症状性溃疡、营养不良性溃疡、热带溃疡、软下疳（例如由淋病（包括尿道炎、宫颈内膜炎和直肠炎）引起的）。与伤口或疮有关的可以能根据本发明成功治疗的病症是烧伤、炭疽、破伤风、气性坏疽、猩红热（scalatina）、丹毒、寻常须疮、毛囊炎、传染性脓胞病或大疱性脓胞病等。术语“伤口”和“溃疡”以及“伤口”和“疮”的使用经常有一定的重叠，而且这些术语常常随机使用。因此，如上所述，在本文中，术语“伤口”包括术语“溃疡”、“损害”、“疮”和“梗死形成”，这些术语是不加区别地使用的，除非另外指出。

待根据本发明治疗的伤口种类还包括：i)一般的伤口，例如外科伤口、外伤、传染性伤口、缺血性伤口、烫伤伤口、化学伤口、大疱伤口；ii)特别针对口腔的伤口，例如拔牙后伤口、特别是与治疗囊肿和脓肿有关的牙髓伤口、细菌、病毒性或自免疫原性溃疡和损害、机械伤口、化学伤口、烫伤伤口、感染性伤口和苔癣样伤口；具体例子是疱疹溃疡、疱疹性口炎、急性坏死性牙疳和口灼伤综合征；和 iii)皮肤上的伤口，例如肿疡、烧伤（例如化学烧伤、烫伤）、损害（细菌性、病毒性、自免疫性）、咬伤和外科切口。其他的伤口分类方法是：i)归因于外科切口、轻微擦伤和轻微咬伤的小的组织损失，或 ii)严重的组织损失。后面的类别包括缺血性溃疡、受压溃疡、瘘、撕裂、严重咬伤、热烧伤和供区伤(在软组织和硬组织中)和梗死形成。

在本发明的其他方面，待预防和/或治疗的伤口选自无菌伤口、梗死形成、挫伤、切伤、撕裂伤、非穿透伤、开放性创伤、贯通伤、穿透伤、刺伤、脓毒性伤口和皮下创伤。

与本发明有关的其它重要伤口是如缺血性溃疡、受压溃疡、瘘、严重咬伤、热烧伤和供区伤的伤口。

在一个实施方案中，本文所述的化合物作为物理治疗/康复的辅药或作为同化剂用于伤口愈合。在另一个实施方案中，本文所述的化合物用于促进前交叉韧带（ACL）或内侧交叉韧带（MCL）损伤的愈合或加速 ACL 或 MCL 术后恢复。在另一个实施方案中，本文所述的化合物用于提高运动能力。在另一个实施方案中，本文所述的化合物用于治疗烧伤。在另一个实施方案中，

本文所述的化合物用于促进软骨再生。在另一个实施方案中，本文所述的化合物用于预防、治疗或逆转与长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、外科手术、充血性心力衰竭、心肌病、烧伤、癌症、COPD相关的分解代谢。在另一个实施方案中，本文所述的化合物用于预防或逆转由创伤引起的蛋白质分解代谢。在另一个实施方案中，本文所述的化合物用作：a) 在外科手术中使用的灼烙疗法（cauterization therapy）（激光或辐射）的辅药以促进伤口愈合，b) 冷冻疗法的辅药以促进伤口愈合，c) 化学疗法的辅药以预防副作用，例如脱发、性腺功能减退症、肌萎缩，骨质减少、骨质疏松症、少肌症、LDL、甘油三酯(TG)或总胆固醇增加、HDL 减少。在另一个实施方案中，本文所述的化合物用于慢性分解代谢状态（昏迷、消耗性病症、饥饿、进食障碍）；并发性骨折和肌肉损害；其中有明显的肌肉或骨消耗的危重病；和/或结缔组织疾病和病症。

缺血性溃疡和压迫溃疡是通常愈合得极慢的伤口，特别在这种情况下，改善而快速的愈合当然对病人很重要。而且，当愈合改善且发生得更快时，治疗罹患这种伤口的患者所涉及的费用显著减少。

供区伤的发生与例如硬组织从身体的一个部位移动至身体的另一个部位（例如移植）有关。由这种手术引起的伤口十分疼痛，因此，改善愈合十分有价值。

术语“皮肤”以非常广泛的意义使用，包括皮肤的表皮层，在皮肤或多或少地损伤的情况下，也包括皮肤的真皮层。除了角质层以外，皮肤的表皮层是外（上皮）层，而较深的皮肤结缔组织层称为真皮。

在一些实施方案中，烧伤与睾酮水平降低相关，而性腺功能减退症与伤口愈合延迟相关。在一个实施方案中，本发明的方法提供治疗罹患伤口或烧伤的个体。

在一些实施方案中，本发明提供用于促进前交叉韧带（ACL）或内侧交叉韧带（MCL）损伤愈合或加速 ACL 或 MCL 术后恢复的方法。

在一些实施方案中，本发明提供用于治疗个体的内分泌病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药、治疗胃肠系统的药、

治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，内分泌病症包括肢端肥大症、艾迪生病、肾上腺疾病、先天性肾上腺增生、雄激素不敏感综合征、先天甲状腺功能减退症、库欣综合征、尿崩症、糖尿病、1 型糖尿病、2 型糖尿病、糖尿病酮症酸中毒、空蝶鞍综合征、内分泌腺肿瘤、内分泌系统疾病、巨人症、性腺障碍、格雷夫斯病、两性同体、醛固酮增多症、高血糖高渗性非酮性昏迷、垂体功能亢进、高催乳素血症、甲状腺功能亢进症、性腺功能减退症、垂体功能减退症、甲状腺功能减退症、卡尔曼综合征、纳尔逊综合征、甲状旁腺疾病、垂体疾病、自身免疫性多内分泌腺病、青春期延迟、早熟青春期、肾性骨营养不良、甲状腺疾病、甲状腺激素抵抗综合征、甲状腺肿瘤、甲状腺结节、甲状腺炎、自身免疫性甲状腺炎、亚急性甲状腺炎或者 Wolfram 综合征。

在一个实施方案中，“性腺功能减退症”是由生殖腺功能性活动异常降低导致的或以其为特征的病症，并伴有生长和性发育延迟。

在一些实施方案中，本发明提供用于治疗个体的泌尿生殖器疾病和/或能育性、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明包含给予个体组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗感染药、治疗肾脏的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，泌尿生殖器疾病和/或能育性疾病包括流产、自发性骨盆粘连、外阴阴道念珠菌病、产后抑郁、妊娠糖尿病、精神性性交困难、难产、子痫、子宫内膜异位症、死胎、胎儿生长迟缓、胎盘破裂过早、女性生殖器疾病、女性生殖器肿瘤、葡萄胎、妊娠剧吐、不孕、卵巢囊肿、卵巢扭转、盆腔炎性疾病、胎盘疾病、胎盘功能不全、多囊卵巢综合征、羊水过多、产后出血、妊娠并发症、异位妊娠、外阴瘙痒、产褥期疾病、产褥感染、输卵管炎、滋养层肿瘤、子宫颈功能不全、子宫内翻、子宫脱垂、阴道疾病、外阴疾病、外阴硬化性苔癣（vulvar lichen sclerosis）。

在一些实施方案中，本发明提供用于治疗个体的血液和/或淋巴疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，血液和/或淋巴疾病包括纤维蛋白原缺乏血症、贫血、再生障碍性贫血、溶血性贫血、先天非球形红细胞性贫血（congenital nonspherocytic anemia）、巨幼细胞贫血、恶性贫血、镰状细胞贫血、肾性贫血、血管淋巴样增生伴嗜酸细胞增多、抗凝血酶 III 缺乏、Bernard-Soulier 综合征、血液凝固障碍、血小板疾病、蓝色橡皮疱样痣综合征、切东二氏综合征、冷球蛋白血症、弥漫性血管内凝血、嗜酸粒细胞增多、Erdheim-Chester 病、胎儿幼红细胞增多症、伊万思综合征、因子 V 缺乏、因子 VII 缺乏、因子 X 缺乏、因子 XI 缺乏、因子 XII 缺乏、范科尼贫血、巨淋巴结增生、血液病、血红蛋白病、阵发性血红蛋白尿、血友病 A、血友病 B、新生儿出血病、组织细胞增多病、朗格汉斯细胞组织细胞增生症、非朗格汉斯细胞组织细胞增生症、乔布综合征、白血球减少症、淋巴结炎、淋巴管平滑肌增多症、淋巴水肿、高铁血红蛋白血症、骨髓增生异常综合征、骨髓纤维化、髓样化生、骨髓增殖性疾病、嗜中性白血球减少症、副蛋白血症、血小板存贮池缺如、真性红细胞增多症、蛋白质 C 缺乏、蛋白质 S 缺乏、紫癜、血小板减少性紫癜症、血栓性血小板减少、RH-同种免疫、结节病、结节病、球形红细胞增多症、脾破裂、地中海贫血、血小板无力症、血小板减少、Waldenstrom 巨球蛋白血症或血管性血友病。

在一些实施方案中，本发明提供用于治疗个体的先天性、遗传性或新生儿疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，先天性、遗传性或新生儿疾病包括艾卡迪综合征、羊膜带综合征、无脑畸形、Angelman 综合征、运动失调性毛细血管扩张症、Bannayan-Zonana 综合征、Barth 综合征、基底细胞痣综合征、贝-威二氏综

合征、布卢姆综合征、腮-耳-肾综合征、猫眼综合征、大脑性巨人症联合畸形综合征（cerebral gigantism-charge syndrome）、染色体 16 异常、染色体 18 异常、染色体 20 异常、染色体 22 异常、Costello 综合征、猫叫综合征、Currarino syndrome 综合征、囊性纤维化病、De Lange 综合征、10q 远侧三体性（distal trisomy 10q）、唐氏综合征、外胚层发育不良症、胎儿酒精综合征、胎儿疾病、胎儿-胎儿输血、脆 X 综合征、弗-谢二氏综合征、腹裂、先天性遗传性疾病、脐疝、前脑无裂畸形、色素失调症、伊维马克综合征、雅各布斯综合征、黄疸、克兰费尔特综合征、拉尔森综合征、劳-穆二氏综合征、无脑回、小头畸形、9p 单体性、指甲膝盖综合征、神经纤维瘤病、神经元蜡样质脂褐质沉积病、努南综合征、Ochoa 综合征(尿路面容综合征（urofacial syndrome），具有古怪面部表情的肾盂积水)、眼脑肾综合征、Pallister-Killian 综合征、帕-魏二氏综合征、Proteus 综合征、梨状腹综合征、Rett 综合征、罗比挠综合征、鲁-塔二氏综合征、脑裂、左右转位、史-伦-奥三氏综合征、Smith-Magenis 综合征、斯特季-韦伯二氏综合征、先天性梅毒、毛发低硫营养不良、三 X 女性、13 三体性(帕塔综合征)、9 三体性、特纳综合征、联体儿、乌谢尔综合征、瓦尔登布尔氏综合征、维尔纳综合征或 Wolf-Hirschhorn 综合征。

在一些实施方案中，本发明提供用于治疗个体的结缔组织疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药物、免疫调节剂、治疗皮肤病症的药、抗感染药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，结缔组织疾病包括强直性脊柱炎、Ehlers-Danlos 综合征、亨诺-许兰氏紫癜、川崎病、马方综合征、结节性多动脉炎、多肌炎、银屑病关节炎、反应性关节炎、类风湿性关节炎、硬皮病、干燥综合征、干眼病、斯蒂尔病、系统性红斑狼疮、塔卡亚萨病或韦格纳肉芽肿病。

在一些实施方案中，本发明提供用于治疗个体的代谢病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗糖尿病药、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的

药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，代谢病包括酸碱平衡失调、酸中毒、碱中毒、尿黑酸尿症、α-甘露糖苷贮积症、先天性氨基酸代谢障碍、淀粉样变、缺铁性贫血、抗坏血酸缺乏、维生素缺乏症、脚气病、生物素酰胺酶缺乏、碳水化合物缺乏糖蛋白综合征、毒碱病症（carnitine disorders）、胱氨酸贮积症、胱氨酸尿、脱水、法布里病、脂肪酸氧化障碍、岩藻糖苷贮积症、半乳糖血症、戈谢病、吉尔伯特病、葡糖磷酸脱氢酶缺乏、戊二酸血症、糖原贮积病、Hartnup 病、血色素沉着病、血铁质、肝豆状核变性、组氨酸血症、同型胱氨酸尿症、高胆红素血症、高钙血症、高胰岛素血症症、高钾血症、高脂血症、高草酸尿、维生素 A 过多症、低钙血症、低血糖症、低钾血症、低钠血症、低磷酸酯酶血症、胰岛素抵抗、碘缺乏、铁超负荷、慢性特发性黄疸、利氏病、莱-奈二氏综合征、亮氨酸代谢障碍、溶酶体贮积病、镁缺乏、枫糖尿病、Melas 综合征、门凯氏卷发综合征、代谢疾病、代谢综合征 X、先天性代谢缺陷、线粒体疾病、粘脂质累积病、粘脂质累积病、尼曼匹克病、肥胖症、鸟氨酸氨甲酰转移酶缺乏症、骨软化症、糙皮病、过氧化物酶体失调、苯丙酮尿、红血球生成性卟啉病、卟啉症、假性早衰、戈谢病、雷夫叙姆病、Reye 综合征、佝偻病、桑德霍夫病、饥饿、丹吉尔病、泰-萨克斯病、四氢生物蝶呤缺乏、三甲胺尿症(trimethylaminuria)、酪氨酸血症、尿素循环障碍、水电解质平衡失调、韦尼克脑病、维生素 A 缺乏病、维生素 B12 缺乏病、维生素 B 缺乏、沃尔曼病或 Zellweger 综合征。

在一些实施方案中，本发明提供用于治疗个体的环境因素诱发疾病（disorder of environmental origin）、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统药物、治疗胃肠系统的药、治疗皮肤病症的药、治疗中枢神经系统的药、抗感染药、治疗肝脏的药、治疗肾脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，环境因素诱发疾病包括耳气压伤、咬伤和蜇伤、脑震荡、烧伤、中心核综合征、颅脑损伤、电击伤、骨折、冻伤、

热应激障碍、晕动病、职业病、中毒、惊吓婴儿综合征、肩损伤、太空运动病、脊髓损伤、蜱性麻痹或伤口(贯通性和非贯通性)。

在一些实施方案中，本发明提供用于治疗个体的行为机制病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和治疗心血管系统的药物、治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中，行为机制病包括攻击、对死亡的态度、共同依赖、自伤行为、性行为或社会行为。

在一些实施方案中，本发明提供用于治疗个体精神障碍、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和治疗中枢神经系统的药物、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，精神障碍包括阿斯佩格综合征、注意力缺陷障碍伴多动、注意力缺陷障碍伴多动、双相型障碍、边缘型人格障碍、替身综合征、儿童行为障碍、战时神经症、循环性情感障碍、依赖性人格障碍、抑郁症、分离型精神障碍、心境恶劣障碍、进食障碍、纵火行为、疑病症、冲动控制障碍、克-列二氏综合征、精神障碍、儿童期诊断的精神障碍、多重人格障碍、米肖森综合征、芒氏综合征、代理明肖森综合征（Munchhausen by proxy）、自恋型人格障碍、发作性睡眠、强迫性障碍、性变态、恐怖症、精神病、不宁腿综合征、精神分裂症、季节性情感障碍、性欲和性表现障碍、心理性性功能障碍、睡眠障碍、躯体型障碍、创伤后应激障碍、物质相关性障碍、自杀行为或者拔毛狂。

在一个实施方案中，“抑郁”指涉及身体、情绪和思维的疾病，其影响人吃饭、睡觉的方式、自我感知和考虑事物的方式的想法。抑郁的体征和症状包括缺乏活动兴趣、食欲缺乏或进食过量、缺乏表情、空虚、感觉绝望、悲观、内疚或无助、社交退缩、疲劳、睡眠障碍、集中、记忆或作决定困难、躁动、易怒、头痛、消化障碍或慢性疼痛。

在一个实施方案中，“认知”指认识的过程，特别是保持清醒、认识、思维、学习和判断的过程。认知涉及心理学、语言学、计算机科学、神经科学、数学、习性学和哲学领域。在一个实施方案中，“情绪”指脾气或精神状态。

如本文所指的，变化指认知和/或情绪的任何积极或消极变化。

在一些实施方案中，本发明提供治疗个体的肝病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、治疗胃肠系统的药、抗感染药、治疗肝脏的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一个实施方案中，肝病包括肝癌、原发性胆汁性肝硬变、自身免疫性肝炎、慢性肝病、肝硬化、肝炎、病毒性肝炎(甲型肝炎、乙型肝炎、慢性乙型肝炎、丙型肝炎、慢性丙型肝炎、丁型肝炎、戊型肝炎、肝炎X)、肝功能衰竭、黄疸、新生儿黄疸、肝细胞瘤、肝癌、肝脓肿、酒精性肝病、血色素沉着病、肝豆状核变性病、门静脉高压、原发性硬化性胆管炎、结节病、绦虫、泡状棘球蚴病、片形吸虫病、血吸虫病、戈谢病、Zellweger综合征、酒精中毒、食物中毒、肺炎球菌性肺炎或者嗜盐弧菌。

在一些实施方案中，本发明提供用于治疗个体的肾疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗胃肠道系统的药、抗感染药、治疗肾脏的药、治疗代谢病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，肾病包括肢端肥大症、急性肾衰竭(ARF)(淀粉样变)、常染色体显性多囊肾病、肾结石、肾脏囊肿、常染色体隐性多囊肾病、慢性肾衰竭(CRF)、慢性肾病、科-勒二氏综合征、肺源性心脏病、冷球蛋白血症、糖尿病肾病、血脂异常、戈谢病、肾小球肾炎、肺出血肾炎综合征、溶血尿毒症综合征、肝炎、肾癌、肾结石、白血病、脂蛋白血症、狼疮、多发性骨髓瘤、肾炎、多动脉性肾囊肿（polyartekidney cysts）、链球菌感染后肾小球肾炎、肾小球肾炎、肾痛、先兆子痫、肾结核、肾盂肾炎、肾小管性酸中毒肾病、链球菌所导致的中毒性休克综合征、血栓栓塞、弓形体病、泌尿道感染、膀胱输尿管反流或者威廉斯综合征。

在一个实施方案中，所述肾疾病或病症是急性的，或者在另一个实施方案中是慢性的。在一个实施方案中，其中可以使用所述治疗方法的肾脏疾病或病症的临床适应症包括管型尿、测量的肾小球滤过率或其它肾功能指标。

在一个实施方案中，本发明的方法用于易患肾疾病或病症的个体。在一个实施方案中，关于个体的短语“易患肾疾病或病症”与短语“处于风险的个体”的同义，其包括处于患急性或慢性肾功能衰竭的风险，或如果合理地预计所述个体将罹患与功能性肾单位进行性损失相关的肾功能进行性损失，则所述个体处于需要肾替代疗法的风险。具体的个体是否处于风险是可以由相关医学或兽医学领域的普通技术人员按常规作出的决定。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度蛋白质能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的生活质量(QOL)分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与性腺功能减退症有关的症状，所述性腺功能减退症在所述个体中由女性雄激素缺乏（ADIF）引起；由老年男性雄激素缺乏（ADAM）（包括疲劳、抑郁、性欲降低、勃起功能障碍、认知下降、情绪下降）引起；由雄激素不足（男性或女性）、雄激素缺乏（男性或女性）引起。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平(>30 mg/天或 20 μg/min)的白蛋白（微量蛋白尿），接着是持续10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的

药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。在一些实施方案中，消耗性疾病包括肌损伤、卧床休养、固定、神经损伤、神经病、糖尿病神经病变、酒精性神经病、脊髓亚急性联合变性、糖尿病、类风湿性关节炎、运动神经元疾病、迪谢内肌营养不良、腕管综合征、慢性感染、结核病、艾迪生病、成人脊髓性肌萎缩（sma）、肢体肌萎缩、酒精性神经病、厌食、神经性厌食、与恶病质相关的厌食、与衰老相关的厌食、后纵隔肿瘤（back tumour）、皮肌炎、髋关节癌、包涵体肌炎、色素失调症、肋间神经痛、幼年型类风湿关节炎、累-卡-佩三氏病、肌萎缩、多灶性运动神经病变、肾病综合征、成骨不全、小儿麻痹症后期综合征、肋骨肿瘤、脊髓性肌萎缩、反射性交感神经营养不良综合征或泰-萨克斯病。

在本文中，消耗性病症或障碍定义为至少部分地以体重、器官质量或组织质量的异常的进行性损失为特征的病症或障碍。消耗性病症可以作为疾病例如癌症的结果而发生，或可归因于生理或代谢状态，例如废用性失调，所述废用性失调可以因长期卧床或当四肢被固定（例如在铸型中）时而发生，或因出现多个伤口（包括例如在糖尿病中出现的截肢、和其它病症）而发生，本领域的技术人员会理解这一点。消耗性病症也可以是年龄相关的。在消耗性病症过程中发生的体重减少的特征可以是总体重的减少或器官重量的减少，例如归因于组织蛋白减少的骨量或肌肉量的减少。

在一个实施方案中，术语“肌萎缩（muscle wasting）”或“肌萎缩（muscular wasting）”指肌肉量的进行性损失和/或肌肉的进行性衰减和退化，包括控制运动的骨骼肌或随意肌和控制心脏的心肌和平滑肌。在一个实施方案中，所述肌萎缩病症或障碍是慢性肌萎缩病症或障碍。“慢性肌萎缩”在本文中定义为肌肉量的慢性（即持续很长一段时间的）进行性损失和/或肌肉量的慢性进行性衰减和退化。

肌萎缩过程中发生的肌肉量损失可以是以由于肌肉蛋白分解代谢造成的肌肉蛋白分解或降解为特征。蛋白质分解代谢因为异常高速的蛋白质降解、异常低速的蛋白质合成或这两种的结合而发生。无论是由高度的蛋白质降解还是低度的蛋白质合成引起的肌肉蛋白分解代谢或消耗都会导致肌肉量的减少和肌萎缩。术语“分解代谢”具有本领域中普遍知晓的含义，特别是指能量燃烧形式的新陈代谢。

肌萎缩可以作为病状、疾病、病症或障碍（包括通过本发明的方法治疗的疾病，例如终末期肾功能衰竭）的结果而发生。

在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的横纹肌溶解、器官衰竭或功能不全的方法。在一些实施方案中，本发明提供用于预防抑制素诱导的肾功能衰竭或肝功能衰竭或不全的方法。在一个实施方案中，所述方法包括向个体给药包含本发明的化合物和抑制素的组合物。

在一个实施方案中，所述消耗性疾病是个体的恶病质或非意愿体重减轻。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏病的个体的肌萎缩的方法。在另一个实施方案中，本发明提供用于治疗、预防、抑制、减少或压制罹患肾脏疾病或病症的个体的蛋白质分解代谢的方法。

恶病质是由疾病引起的或作为疾病副反应的虚弱和体重减少。由于疾病或损伤而长期住院或例如当肢体被固定时发生的废用性失调也能导致肌萎缩。研究显示，长期住院的罹患损伤、慢性病、烧伤、创伤或癌症的患者中，出现长期单侧肌萎缩和由此引起的体重减少。神经系统损伤，例如本文进一步叙述的脊髓损伤，也可能是致病因素。

在一些实施方案中，本发明提供用于治疗个体的消耗性疾病或病症、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在另一个实施方案中，所述消耗性疾病和病症尤其包括：a) 获得性免疫缺陷综合征（AIDS）消耗；b) 与卧床休息有关的消耗；c) 贪食症和/或与贪食症有关的消耗；d) 恶病质；e) 癌症恶病质；f) HIV 消耗；g) 由以下因素引起的减轻体重的恶病质和蛋白质损失：长期的危重病、肺功能障碍、呼吸机依赖、衰老、AIDS、创伤、充血性心脏衰竭、心肌病、烧伤、癌症、慢性阻塞性肺疾病（COPD）、进食障碍例如贪食病、神经性厌食、食欲缺乏、饥饿和/或抑郁。

在一些实施方案中，本发明提供用于治疗个体的无效状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述无效状态是小儿麻痹症后期综合征。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和免疫调节

剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠道系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、维生素或它们的组合。

在一些实施方案中，本发明用本发明的化合物提供辅助治疗。例如，在一个实施方案中，在疾病、障碍或病症的治疗（其中使用锻炼和限制饮食）中，给药本发明的化合物包括在这种治疗方案中。例如，在一个实施方案中，如本领域的技术人员将认识的，用本发明的化合物进行的辅助疗法或治疗，结合限制饮食和/或锻炼的，可能是用于治疗胰岛素抵抗、葡萄糖耐受不良、体重减轻、糖尿病、心血管疾病、代谢综合征、癌症、肌萎缩等的疗法。

在一些实施方案中，本发明提供用于治疗个体的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的性腺功能减退状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，性腺功能减退症是由治疗引起的，所述治疗改变激素自女性和男性性腺的分泌。在一些实施方案中，性腺功能减退症可能是“原发性的”或“中枢性的”。在原发性性腺功能减退症症中，卵巢或睾丸本身不正常地发挥作用。在一些实施方案中，性腺功能减退症可能是由外科手术、辐射、遗传性病症和发育障碍、肝病和肾病、感染或某些自免疫疾病诱导的。在一些实施方案中，绝经是性腺功能减退症的形式。在一些实施方案中，绝经可能导致闭经、热潮红、阴道干燥或归因于女性雌激素水平下降的易激惹。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的骨质减少状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中，骨质减少是骨量的轻微减少。在一些实施方案中，骨质

减少是骨质疏松症的前兆。在一些实施方案中，骨质减少定义为比正常年青成人的骨密度低 1-2.5 个标准偏差（SD）的骨密度。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，本发明提供用于治疗个体的药物治疗诱导的少肌状态、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一些实施方案中少肌症是严重的肌肉量减少。在一个实施方案中，少肌症的定义是具有比低于正常年青成人的平均值 2 个标准偏差更低的瘦体重。在一些实施方案中，少肌症由以下原因引起：遗传因素、循环系统改变、毛细管:肌纤维比率降低、运动神经元改变、去神经支配、运动神经末梢板衰退、I 型纤维选择性神经移植术、造成肌肉损害的炎症应答、运动减少、营养不良、低膳食蛋白摄入量、维生素 D 缺乏、年龄相关的维生素 D 减少、氧化性应激、肌肉线粒体突变、特定类型肌纤维的改变、肌肉蛋白减少、致残疾病、卒中、阿尔茨海默氏病、帕金森病、骨质疏松症、动脉粥样硬化、糖尿病、高胰岛素血症、肾功能衰竭或性腺功能减退症。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含 SARM 化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

在一些实施方案中，本发明提供用于治疗个体的如上文所述的疾病和/或病症的组合、降低其发病率、延缓其发作或进展、或减轻和/或消除与其相关的症状的方法。在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的

药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素或它们的组合。

应该理解，如本文所述的本发明的任何方法都包括向个体给药本文所述的化合物或包含它的组合物，以治疗所指的疾病、障碍或病症。每一种本文所述的方法和/或其全部还可能包括给药本文所述的其它治疗剂，本领域的技术人员会理解这一点。

在一些实施方案中，本发明提供用于促进例如乳、精子或卵细胞的产生的方法。在一些实施方案中，本发明提供用于促进瘦肉或卵细胞的产生的方法。在一些实施方案中，本发明提供用于提高饲喂或配种牲畜的生产力的方法，例如增加精子计数、改善精子形态等。在一些实施方案中，本发明提供用于延长农场动物（例如产蛋母鸡、产奶奶牛等）的生产期和/或提高兽群健康（例如改善免疫清除、强壮动物）的方法。

在一个实施方案中，所述方法包括向个体给药组合物，所述组合物包含本发明的化合物和抗癌药、免疫调节剂、抗糖尿病药、治疗心血管系统的药、治疗胃肠系统的药、治疗中枢神经系统的药、治疗代谢病的药、治疗消耗性疾病的药、基因治疗剂、治疗内分泌系统的药、治疗皮肤病症的药、抗感染药、治疗肝脏的药、治疗肾脏的药、维生素、营养添加剂、激素（每一种和/或全部均如本文所述）、或如本文所述的任何其它治疗剂、或它们的组合。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：囊性纤维化病及由其引起的诱导性性腺功能减退状态、癫痫及由其引起的诱导性性腺功能减退状和/或代谢亢进状态、遗传性血管性水肿、红斑狼疮及由其引起的 BMD 下降、饮酒和抽烟诱导的骨质疏松症，所述方法包括向所述个体给药本文所述的 SARM。

在另一个实施方案中，本发明提供用于治疗个体的以下疾病的方法：小儿麻痹症和小儿麻痹后综合征及其它无效状态、抑制素诱导的横纹肌溶解症、抑制素诱导的肌无力、抑制素诱导的器官衰竭或功能不全，所述方法包括给药本文所述的化合物和任选适当的抑制素（本本领域的技术人员会理解这一点），和/或任何治疗剂。

在另一个实施方案中，本发明提供用于治疗阿片样物质诱导的雄激素缺乏（OPIAD）的方法，所述方法包括向个体给药本文所述的化合物和任选地

阿片剂、阿片样物质、麻醉药等、美沙酮、长效阿片剂/阿片样物质例如 Kadian、缓释吗啡（所有阿片剂/阿片样物质/麻醉药均获得 FDA 批准）、用于治疗海洛因成瘾的阿片剂/阿片样物质、用于治疗恶性肿瘤慢性疼痛的阿片剂/阿片样物质、用于治疗非恶性肿瘤的慢性疼痛综合征的阿片剂/阿片样物质。

在另一个实施方案中，本发明提供用于治疗神经系统疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选的抗精神病药（例如佐替平、氟哌啶醇、氨磺必利、利培酮、其它多巴胺 D2 受体拮抗剂）、抗癫痫病药物（例如丙戊酸、卡马西平、奥卡西平（oxcarbamazepine）等）或它们的组合物。

在另一个实施方案中，本发明提供用于治疗激素依赖性疾病、障碍或病症的方法，所述方法包括向所述个体给药本文所述的化合物和任选地化疗剂和治疗（甲氨蝶呤、环磷酰胺、异环磷酰胺、阿霉素、多柔比星、糖皮质激素、环孢菌素、L-甲状腺素、SERM、抗炎药、氟维司群、GnRH 剂、ADT、中止激素替代疗法、颅脑照射、周边照射（peripheral irradiation）等；诱导高催乳素血症（prolactinemia）的药物治疗（通过 5HT2 受体作用的血清素能性的抗抑郁剂、选择性血清素再摄取抑制剂、单胺氧化酶抑制剂、三环抗抑郁剂、抗高血压药例如甲基多巴、利血平、可乐定和维拉帕米；抗多巴胺能的止吐药例如甲氧氯普胺，H2 受体拮抗剂例如西咪替丁和雷尼替丁，雌激素，苯丙胺，AR 部分拮抗剂（酮康唑、螺内酯、依普利酮）

在另一个实施方案中，如本文所述的本发明的化合物和组合物用于促进或加速手术操作后恢复。

在一个实施方案中，本发明提供本文所述的化合物用于减少个体的脂肪量的用途。在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的这种使用方法。

在另一个实施方案中，本发明提供本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合或者含有它们的组合物的以下用途：治疗腹部脂肪累积；治疗肥胖性少肌症；改善身体成分；减少体脂含

量；减少脂肪量；改善血脂谱（profile），增加肌肉量/肌肉强度/肌肉功能；增加骨量/BMD/骨强度/骨功能；减少体脂；先天性高胰岛素血症；库欣病（高皮质醇血症（hypercortisolemia））；个体的与代谢综合征相关的肥胖症或糖尿病。

在另一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

在一个实施方案中，本发明提供本文所述的化合物用于增加个体的瘦体重的用途。在另一个实施方案中，这种用途包括给药本文所述的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合。

在一个实施方案中，所述个体患有激素失调、激素病症或激素疾病。在另一个实施方案中，所述个体处于绝经。

实施例 15 显示，式(I)的化合物是合成代谢性的，但是其雄激素性最低，因此，这种化合物可以用于治疗过去雄激素是禁忌的患者群。无论睾酮是否存在，式(I)的化合物都显示促进肌肉生长，同时对前列腺施加抗增殖作用，因此，在一个实施方案中，本发明的方法用于恢复患有少肌症或恶病质的个体损失的肌肉量。

在一个实施方案中，本文所述的化合物改变个体的瘦素水平。在另一个实施方案中，本文所述的化合物降低瘦素的水平。在另一个实施方案中，本文所述的化合物增加个体的瘦素水平。已知瘦素对肥胖症小鼠的食欲、体重减轻有影响，因此其已与肥胖症有关。

在一个实施方案中，本文所述的化合物影响瘦素的循环水平，在另一个实施方案中，影响瘦素的组织水平。在一个实施方案中，术语“瘦素的水平”指瘦素的血清水平。如本文所指的，本发明的化合物对体外和体内的瘦素有影响。瘦素的水平可以用本领域的技术人员已知的方法来测定，例如通过可商购的 ELISA 试剂盒来测定。而且，可以通过本领域技术人员已知的任何方法在体外测定或体内测定中测定瘦素的水平。

由于瘦素与控制食欲、减轻体重、摄取食物和能量消耗有关，所以，调节和/或控制瘦素的水平是治疗、预防、抑制罹患肥胖症个体的肥胖症、降低其发病率的有用的治疗方法。调节瘦素的水平可以导致缺乏食欲、减少食物

摄取、增加瘦素个体的能量消耗，因此，可能有利于控制和治疗肥胖症。

在一个实施方案中，术语“肥胖症”定义为由脂肪在身体内过度累积导致体重增加超过骨骼的限制和身体的需要

在一个实施方案中，术语“肥胖症相关的代谢失调”指由肥胖症引起的、作为肥胖症的后果的、因肥胖症而加重的或继发于肥胖症的病症。这种病症的非限制性的例子是骨关节炎、II 型糖尿病、血压增加、卒中和心脏病。

胆固醇、甘油三脂和其它脂质通过脂蛋白在体液中运输，所述脂蛋白可以根据它们的密度划分为例如极低密度脂蛋白（VLDL）、中密度脂蛋白（IDL）、低密度脂蛋白（LDL）和高密度脂蛋白（HDL）。

已显示，LDL-胆固醇在血液中的高水平与动脉粥样硬化有关，动脉粥样硬化是部分地以脂质在动脉特别是冠状动脉的内壁中沉积为特征的进行性疾病。而且已经显示，也 LDL-胆固醇的高血液水平与冠心病有关。而且，HDL 胆固醇的血液水平与冠心病之间存在负相关。

血液中的总胆固醇水平（其为 HDL-胆固醇、LDL-胆固醇、VLDL-胆固醇和乳糜微粒-胆固醇的总和）不一定是冠心病和动脉粥样硬化风险的预兆。

但是，动脉粥样硬化和 LDL 胆固醇水平之间的关联比动脉粥样硬化和总血清胆固醇水平之间的类似关联高得多。

在一个实施方案中，本发明提供将本文所述的化合物用于改善个体的脂质谱和/或减少循环脂质水平的使用方法。在一些实施方案中，根据本发明的这一方面，所述个体罹患选自以下的一种或多种病症：动脉粥样硬化症及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病和高血糖症，而且本发明用于给药本文所述的化合物或含有它的组合物，在一些实施方案中，所述化合物或组合物积极地影响所述个体的脂质谱，这是所述方法用于治疗所指的疾病、障碍和病症的一种手段。

在一个实施方案中，本发明提供治疗动脉硬化症及其相关疾病，例如心血管病症、脑血管障碍、周围血管病症、肠血管病症或它们的组合。

在一个实施方案中，心血管病症包括高血压（HTN）、冠脉疾病（CAD）或心肌灌注。在另一个实施方案中，本发明提供本文所述的 SARM 化合物用于促进主动脉平滑肌细胞增殖的使用方法。在另一个实施方案中，本发明提

供本文所述的化合物用于治疗动脉粥样硬化的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于降低血压的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于治疗心脏疾病和病症（包括心肌病、心功能不全例如心肌梗死、心脏肥大和充血性心力衰竭（cognitive heart failure））的使用方法。在另一个实施方案中，本发明提供本文所述的化合物用于保护心脏（包括在胰岛素抵抗中的保护心脏）的使用方；治疗 I 型和 II 型糖尿病、代谢综合征、X 综合征和/或高血压的使用方法。

在一个实施方案中，本发明提供用于治疗、预防个体的心血管和/或脑血管疾病、降低其死亡风险的方法，所述方法包括给药式(I)的化合物或其前药、类似物、异构体、代谢产物、衍生物、药学上可接受的盐、药品、多晶型物、晶体、不纯物、*N*-氧化物、水合物或它们的任意组合、或者含有它们的药物组合物。在一个实施方案中，所述化合物以式(I) 的结构为特征。

在一个实施方案中，式 I 的化合物降低 LDL 和总胆固醇的水平。在另一个实施方案中，式(I)的化合物降低个体的 LDL 和总胆固醇的水平。

在另一个实施方案中，式 I 的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，式(I)的化合物与升高 HDL 的药剂联合给药。在另一个实施方案中，升高 HDL 的药剂包括烟酸。在另一个实施方案中，所述升高 HDL 的药剂包括贝特类，所述贝特类包括吉非贝齐（Lopid）、硫脲系吉非贝齐类似物和非诺贝特（TriCor）。在另一个实施方案中，升高 HDL 的药剂包括他汀类药物。在另一个实施方案中，升高 HDL 的药剂包括 1-羟基烷基-3-苯硫脲及其类似物。

在一个实施方案中，本发明提供用于降低个体的循环脂质水平的方法，所述方法包括给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物。在一个实施方案中，所述个体罹患动脉粥样硬化及其相关疾病、过早衰老、阿尔茨海默氏病、卒中、中毒性肝炎、病毒性肝炎、周围血管功能不全、肾病、高血糖或它们的任意组合。

在一个实施方案中，本发明提供用于治疗个体的动脉粥样硬化及其相关疾病（例如心血管病症、脑血管障碍、周围血管病症或肠血管病症）的方法，所述方法包括向所述个体给药式 I 的化合物或其药学上可接受的盐、水合物、*N*-氧化物或它们的任意组合、或者含有它们的组合物的步骤。所述方法还可

以包括同时、随后或在先给药已知可用于治疗心血管疾病、脑血管障碍、周围血管病症或肠血管病症的一种或多种药剂。

在一个实施方案中，本发明提供改善个体的灵活性和运动的方法，例如通过治疗所述个体的关节炎。

在另一个实施方案中，术语“关节炎”指主要发生在老年人中的非炎性退行性关节病，它以关节软骨变性、骨头及边缘肥大、滑膜改变等为特征。在另一个实施方案中，它还伴有疼痛和僵硬，特别是在长期活动之后。

在一个实施方案中，术语“糖尿病”指胰岛素的相对或绝对缺乏，导致不受控制的糖代谢。大多数患者在临床上可被划分为患胰岛素依赖型糖尿病（IDDM 或 I 型糖尿病）或非胰岛素依赖型糖尿病（NIDDM 或 II 型糖尿病）。

在其它实施方案中，术语“血压增加”或“高血压”指在超过 90/140 mmHg 的重复性高血压。慢性高血压可以造成眼底血管改变、心肌增厚、肾功能衰竭和脑损害。

在其它实施方案中，术语“卒中”指由于供血不足引起脑神经细胞损害，所述供血不足经常由血管破裂或血凝块造成。在其它实施方案中，术语“心脏病”指心脏正常功能和活动发生障碍，包括心力衰竭。

而且，最近显示，雄激素涉及多能间质细胞定型为肌源性谱系并阻止分化为成脂谱系（Singh 等人, Endocrinology, 2003，7 月 24 日）。因此，所述化合物可用于本文所述的阻止脂肪生成和/或改变干细胞分化的方法。

在另一个实施方案中，本发明涉及加速、增加或促进个体减轻体重的方法，所述方法包括向所述个体给药有效加速、增加或促进所述个体减轻体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体的食欲的方法，所述方法包括向所述个体给药有效降低、压制、抑制或减少所述个体的食欲的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的身体成分的方法，所述方

法包括向所述个体给药有效改变所述个体的身体成分的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。在一个实施方案中，改变所述身体成分包括改变所述个体的瘦体重、去脂体重或它们的组合。

在另一个实施方案中，本发明涉及改变个体的瘦体重或去脂体重的方法，所述方法包括向所述个体给药有效改变所述个体的瘦体重或去肪体重的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及将个体的脂肪转化为瘦肌肉的方法，所述方法包括向所述个体给药有效将所述个体的脂肪转化为瘦肌肉的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及治疗个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效治疗所述个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的方法，所述方法包括向所述个体给药有效预防、压制、抑制或减轻个体的肥胖症相关的代谢失调的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合的步骤。

在一个实施方案中，所述肥胖症相关的代谢失调是高血压。在另一个实施方案中，所述病症是骨关节炎。在另一个实施方案中，所述病症是II型糖尿病。在另一个实施方案中，所述病症是血压增加。在另一个实施方案中，所述病症是卒中。在另一个实施方案中，所述病症是心脏病。

在另一个实施方案中，本发明涉及降低、压制、抑制或减少个体脂肪形

成的方法，所述方法包括向所述个体给药本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在另一个实施方案中，本发明涉及改变个体的干细胞分化的方法，所述方法包括向所述个体给药有效改变所述个体的干细胞分化的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体、或它们的任意组合的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻肥胖症；b) 加速、增加或促进减轻体重；c) 降低、压制、抑制或减少食欲；d) 改变身体成分；e) 改变瘦体重或去脂体重；f) 将脂肪转化为瘦肌肉；g) 治疗、预防、压制、抑制或减轻肥胖症相关的代谢失调，例如高血压、骨关节炎、糖尿病、青春晚期糖尿病（MODY）、血压增加、卒中或心脏病；h) 降低、压制、抑制或减少脂肪形成；i) 改变干细胞分化；和/或 j) 改变瘦素水平。

在一个实施方案中，本文所述的化合物用于治疗或中止糖尿病的进展或治疗糖尿病症状。在另一个实施方案中，本文所述的化合物用于治疗与糖尿病相关的并发症。这些病症包括：高血压（HNT）、脑血管病、冠状动脉粥样硬化性心脏病、黄斑变性、糖尿病视网膜病（眼病）和失明、白内障一全身性炎症（以炎症指标例如红细胞沉降率或 C 反应蛋白的增加为特征）、出生缺陷、与妊娠有关的糖尿病、先兆子痫和妊娠高血压、肾病（肾功能不全、肾功能衰竭等）、神经疾病（糖尿病神经病变）、浅表和全身性真菌感染、充血性心力衰竭、痛风/高尿酸血症、肥胖症、高甘油三酯血症、高胆固醇血症、脂肪肝症（非酒精性脂肪性肝炎或 NASH）、以及糖尿病相关的皮肤病例如糖尿病脂性渐进环死（NLD）、糖尿病大水疱（糖尿病性大疱症）、发疹性黄瘤、Digital Sclerosis、播散性环状肉芽肿和黑棘皮病。

在一个实施方案中，本发明提供治疗、压制、抑制以下人类个体的疾病、或降低其发病率的方法：(a) I 型糖尿病；(b) II 型糖尿病；(c) 葡萄糖耐受不良；(d) 高胰岛素血症；(e) 胰岛素抵抗；(f) 肾病；(g) 糖尿病神经病变；(h) 糖尿病视网膜病；(i) 脂肪肝症；(j) MODY 和(k) 心血管疾病，所述方法包

括向所述个体给药式(I)的化合物的步骤。

在一些实施方案中，本文所述的化合物和/或包含它们的组合物可以用于与患糖尿病的个体相关的疾病或病症的应用或治疗。在一个实施方案中，寻求通过本发明的方法治疗的个体是患有 I 型糖尿病的个体。I 型糖尿病以胰腺 β 细胞的自身免疫破坏为特征。90%的个体在诊断时出现所述 β 细胞的免疫破坏标志，所述标志包括胰岛细胞（ICA）抗体、谷氨酸脱羧酶（GAD）抗体和胰岛素(IAA)抗体。尽管这种形式的糖尿病通常发生于儿童和青少年中，但是它可以发生于任何年龄。年轻个体的通常具有快速的 β 细胞破坏并与同时存在酮症酸中毒，而成年人经常保持充足的胰岛素分泌以防止酮症酸中毒达许多年。最终，所有 I 型糖尿患者需要胰岛素疗法以保持血糖量正常。

在一个实施方案中，本发明提供治疗 II 型糖尿病的方法。II 型糖尿病以胰岛素抵抗为特征，而且在该疾病发病的某个阶段以胰岛素分泌相对不足为特征。血浆胰岛素浓度（禁食和膳食刺激的）的绝对值通常增加，但是“相对于”胰岛素抵抗的严重性，血浆胰岛素浓度不足以维持正常的葡萄糖稳态。然而，随着时间推移，出现进行性 β 细胞衰竭，接着发生胰岛素绝对值不足。大多数患有 II 型糖尿病的个体表现出腹内性（内脏性）肥胖症、与胰岛素抵抗的存在密切相关的脂肪肝。所述患者的肝脏变成胰岛素抵抗性，糖原分解不受控制，结果是增加的、非生理性的葡萄糖被输送至血液中。肝脏产生的胆固醇和 VLDL 颗粒也不受控制。而且，这些个体通常存在高血压、血脂异常（高甘油三酯水平和低 HDL-胆固醇水平；餐后高脂血症）和 PAI-1 水平升高。这一连串异常被称为“胰岛素抵抗综合征”或“代谢综合征”或肥胖症相关的病症。由于这些异常，II 型糖尿病的患者罹患大血管并发症例如心肌梗死和卒中的风险增大。

在一个实施方案中，本发明提供治疗糖尿病肾病的方法。糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（>30 mg/天或 20 μg/min）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病患者，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的

肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

在一个实施方案中，本发明提供治疗糖尿病神经病变的方法。糖尿病神经病变是由糖尿病引起的神经病症家族。糖尿病神经病变造成手、臂、足和腿麻木，有时造成它们疼痛和无力。糖尿病中的神经病学问题可能发生于每一个器官系统，包括消化道、心脏和生殖器。糖尿病神经病变划分为周围神经病变、自主神经病变、近端神经病变的和局灶性神经病变。周围神经病变造成趾、足、腿、手和臂的疼痛或感觉缺失。自主性神经病变造成消化、肠和膀胱功能、性反应和出汗的变化，也可影响服务心脏和控制血压的神经。近端神经病变造成股、髋或臀疼痛并导致腿无力。局灶性神经病变导致一条神经或一组神经的突然衰弱，造成肌无力或肌痛。身体内的任何神经都可能受影响。

在一个实施方案中，本发明提供治疗糖尿病视网膜病的方法。糖尿病对眼的影响称为糖尿病视网膜病。糖尿病患者更可能罹患眼疾，例如白内障和青光眼。糖尿病视网膜病对视觉的影响变化很广，取决于该疾病的阶段。糖尿病视网膜病的一些共有症状是视力模糊（这经常与血糖水平有关）、漂浮物（floaters）和闪烁（flashes）以及视力突然丧失。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有葡萄糖耐受不良的个体。葡萄糖耐受不良是糖尿病前期，其中，血糖高于正常水平，但没有高到确保诊断为糖尿病。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有高胰岛素血症的个体。高胰岛素血症是导致胰腺分泌过量胰岛素的潜在问题的征兆。高胰岛素血症的最普遍的原因是胰岛素抵抗，在这种病症中，你的身体对抗胰岛素的效应，而胰腺试图通过产生更多胰岛素来补偿。高胰岛素血症与 II 性糖尿病有关。

在一个实施方案中，寻求通过本发明的方法治疗的个体是患有胰岛素抵抗的个体。胰岛素抵抗是其中正常量的胰岛素不足以使脂肪细胞、肌细胞和肝细胞产生正常的胰岛素反应的病症。脂肪细胞中的胰岛素抵抗造成储存的甘油三酯水解，这提高血浆中游离脂肪酸的水平。肌肉中的胰岛素抵抗减少葡萄糖的摄入，而肝脏中的胰岛素抵抗减少葡萄糖储存，这两种效应帮助提

高血糖。归因于胰岛素抵抗的高水平的血浆胰岛素是葡萄糖经常导致代谢综合征和 II 型糖尿病。

糖尿病和肝肥胖症一般与游离脂肪酸（FFA）水平升高有关，游离脂肪酸促进靶组织中的脂质蓄积和胰岛素抵抗，即主要减弱胰岛素在骨骼肌和肝脏中的作用。胰岛素的突出作用是减少自肝脏的葡萄糖输出。FFA 刺激肝脏糖异生，只要糖异生与肝糖原分解降低平行进行（被称为"肝自身调节"的补偿过程），糖异生本身不会导致肝脏葡萄糖输出增加。FFA 刺激胰岛素分泌，而胰岛素通过抑制胰高血糖素（糖原分解的诱导物）的分泌部分地阻止糖原分解。然而，长期高水平的 FFA 导致肝脏胰岛素抵抗，并因此破坏肝自身调节，导致肝葡萄糖产生增加和罹患 II 型糖尿病。脂肪肝和肝脏胰岛素抵抗是高血糖和 II 型糖尿病的主要驱动力。

在一个实施方案中，本发明提供抑制（改善）脂肪肝的方法，所述方法肝中的胰岛素抵抗被抑制（改善），由此解决 II 型胰岛素的基本问题。

在另一个实施方案中，所述糖尿病是 I 型糖尿病。在另一个实施方案中，所述糖尿病是 II 型糖尿病。

在一个实施方案中，本发明提供治疗、压制、抑制人类个体的糖尿病、降低其发病率的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在另一个实施方案中，所述糖尿病是 I 型糖尿病。在另一个实施方案中，所述糖尿病是 II 型糖尿病。

在一个实施方案中，本发明提供治疗患有葡萄糖耐受不良的人类个体的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的高胰岛素血症的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的胰岛素抵抗的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病肾病的方法，所

述方法包括向所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病神经病变的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的糖尿病视网膜病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的脂肪肝症的方法，所述方法包括所述个体给药式 I 的选择性雄激素受体调节剂化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供治疗人类个体的血管疾病的方法，所述方法包括向所述个体给药式 I 的化合物或其异构体、药学上可接受的盐、药品、水合物、*N*-氧化物或它们的任意组合的步骤。

在一个实施方案中，本发明提供用于 a) 治疗、预防、压制、抑制动脉粥样硬化，b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害的方法，所述方法包括向所述个体给药有效治疗、预防或抑制动脉粥样硬化和归因于脂肪沉积的肝损害的量的本文所述的化合物和/或其类似物、衍生物、异构体、代谢产物、药学上可接受的盐、药品、水合物、*N*-氧化物、前药、多晶型物、晶体或它们的任意组合、或者含有它们的组合物的步骤。

在一个实施方案中，本文所述的化合物用于：a) 治疗、预防、压制、抑制或减轻动脉粥样硬化；b) 治疗、预防、压制、抑制归因于脂肪沉积的肝损害。

在一个实施方案中，动脉粥样硬化指可能从损害动脉最内层开始的慢性复杂疾病。在另一个实施方案中，损害动脉壁的原因可能包括：a) 血液胆固醇水平提高；b) 高血压；c) 烟草烟雾；d) 糖尿病。在另一个实施方案中，吸烟者的这一病症是可治疗的，尽管烟草烟雾可能会使动脉粥样硬化严重恶化并加速其在冠状动脉、大动脉和腿部动脉中的发展。类似地，在另一个实施方案中，本发明的方法可以用于治疗具有早年心血管疾病家族史的个体（其患动脉粥样硬化的风险增加）。

在一个实施方案中，归因于脂肪沉积的肝损害指脂肪在肝细胞中累积形成脂肪肝，脂肪肝可能与肝脏的炎症有关或可能导致肝脏炎症。这可以导致肝的瘢痕形成和硬化。当结瘢痕形成变为广泛性时，其称为肝硬化。

在另一个实施方案中，脂肪在肝脏中蓄积成为肥胖症。在另一个实施方案中，脂肪肝也与糖尿病、高血甘油三酯和大量饮酒有关。在另一个实施方案中，脂肪肝可能伴随某些疾病例如结核病和营养不良、治疗肥胖症的肠分流术、体内维生素 A 过量或使用某些药物比如丙戊酸（商品名：Depakene/Depakote）和皮质类固醇（可的松、泼尼松）而发生。有时脂肪肝作为妊娠并发症发生。

在一个实施方案中，患有肾病的个体，特别是患有终末期肾脏疾病（ESRD）的男性个体罹患性腺功能减退症，其中一些患有伴发的中度至重度的蛋白质-能量营养不良（PEM），其造成更高的促红细胞生成素（EPO）需要量，更低的 QOL 分数和更高的死亡率。许多人具有与性腺功能减退症有关的其它症状，包括疲劳、缺乏食欲、肌无力等。在一些实施方案中，本发明的治疗方法用于治疗与由所述个体的肾脏疾病或病症引起的性腺功能减退症有关的症状。

在一个实施方案中，糖尿病肾病是糖尿病的并发症，其进展得很早，通常在做出糖尿病的临床诊断之前。肾病变最早的临床证据是尿中出现低（但异常）水平（>30 mg/天或 20 μg/min）的白蛋白（微量蛋白尿），接着是持续 10-15 年的蛋白尿（>300 mg/24 h 或 200 μg/min）。在 1 型糖尿病个体，糖尿病性高血压通常在病人罹患微量蛋白尿之前或直到病人罹患微量蛋白尿时就十分明显。一旦出现明显的肾病变，肾小球滤过率（GFR）在一段时间（可能是几年）内下降，造成糖尿病个体的终末期肾脏疾病（ESRD）。

高血压是肾脏病的另一种共病因素。在一些实施方案中，根据本发明治疗肾脏病可以包括用本发明的化合物和治疗高血压的药剂进行同步治疗。

可以用本文所述的化合物和/或组合物，包括本发明的方法治疗的雄激素依赖性病症包括与衰老相关的病症。在一个实施方案中，本文所述的化合物用于：a) 年龄相关的功能下降（ARFD）；b) 逆转或预防 ARFD；c) 逆转或预防老年人 ARFD；d) 逆转或预防 ARFD 引发的少肌症或骨质减少；e) 男性更年期、男性更年期血管舒缩综合征；f) 男性更年期乳腺发育、肌肉强度

/功能；g) 骨强度/功能；h) 愤怒；i) 无力；j) 慢性疲劳综合征；k) 认知损害；和/或 l) 改善认知功能。

在一个实施方案中，本文所述的化合物用于治疗炎症和相关病症，例如：a) 预防、治疗或逆转关节炎；b) 预防、治疗或逆转关节炎性病症，例如贝切特氏病(自动免疫性血管炎)、滑囊炎、二羟焦磷酸钙晶体沉积症(或假性痛风) (CPPD)、腕管综合征、结缔组织病症、克罗恩病、埃-当二氏综合征(EDS)，纤维肌痛、痛风、感染性关节炎、炎症性肠病(IBD)、少年关节炎，系统性红斑狼疮(SLE)、莱姆病、马方综合征、肌炎、骨关节炎、结节性多动脉炎、风湿性多肌痛、银屑病、银屑病关节炎、雷诺现象、反射性交感神经营养不良综合征、莱特综合征、类风湿性关节炎、硬皮病、干燥综合征、肌腱炎或溃疡性结肠炎；c) 预防、治疗或逆转自身免疫性疾病。

在一个实施方案中，本文所述的化合物用于预防医源性作用，包括急性疲劳综合征（手术后）或雄激素剥夺治疗（ADT）诱导的副反应，例如肌肉量减少、肌肉强度降低、脆弱、性腺功能减退症、骨质疏松症、骨质减少、BMD 降低和/或骨量减少。

在一个实施方案中，所述化合物和/或组合物和/或它们的使用方法用于治疗人类个体，其中，在一个实施方案中，所述个体是男性，或在另一个实施方案中，所述个体是女性。

在一个实施方案中，本发明的方法包括给药作为唯一活性成分的本发明的化合物。然而，用于以下的方法也包含在本发明的范围内：糖尿病和相关病症、激素疗法、干眼病、肥胖症、治疗前列腺癌、延缓前列腺的进展、以及预防和/或治疗前列腺癌的复发、男性避孕；治疗骨质疏松症、治疗与 AIDF 相关的病症以及治疗和/或预防慢性肌萎缩，所述方法包括联合一种或多种治疗剂给药所述化合物。这些药剂包括但不局限于：LHRH 类似物、可逆的抗雄激素、抗雌激素药、抗肿瘤药、5-α 还原酶抑制剂、芳香酶抑制剂、孕激素、通过其它细胞核激素受体作用的药剂、选择性雌激素受体调节剂（SERM）、孕激素、雌激素、PDE5 抑制剂、阿扑吗啡、二碳磷酸盐化合物和一种或多种其它的 SARM。

因此，在一个实施方案中，本发明的方法包括联合糖尿病药物（例如曲格列酮、罗格列酮和吡格列酮）给药本发明的化合物。在另一个实施方案中，

本发明的方法包括联合 LHRH 类似物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合可逆的抗雄激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗雌激素药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合抗癌药给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 5-α 还原酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合芳香酶抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合通过其它细胞核激素受体作用的药剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合选择性雌激素受体调节剂（SERM）给药所述的化合物。在另一个实施方案中，本发明的方法包括联合孕酮给药所述的化合物。在另一个实施方案中，本发明的方法包括联合雌激素给药所述的化合物。在另一个实施方案中，本发明的方法包括联合 PDE5 抑制剂给药所述的化合物。在另一个实施方案中，本发明的方法包括联合阿扑吗啡给药所述的化合物。在另一个实施方案中，本发明的方法包括联合二碳磷酸盐化合物给药所述的化合物。在另一个实施方案中，本发明的方法包括联合一种或多种其它 SARM 给药所述的化合物。在一些实施方案中，本发明的方法包括联合制剂，所述制剂包含所述的化合物和上文所述的药剂。在一些实施方案中，例如为了应对部分待治疗患者亚群的需要或单个患者的需要，所述联合制剂可以变化，所述不同的需要可能归因于具体疾病、所述疾病的严重性、年龄、性别或体重，这可以由本领域的技术人员容易地确定。在一些实施方案中，本发明的方法包括处理单个患者的需要的个性化用药方法。在一个实施方案中，不同的需要可归因于具体疾病、所述疾病的严重性、患者的整体医学状态或所述患者的年龄。在一些实施方案中，个性化用药是应用基因组数据以更好地定向医学干预的递送。在一些实施方案中，个性化用药方法用作发现和临床测试本发明的新产品的工具。在一个实施方案中，个性化用药包括应用临床上有用的诊断工具，所述工具可能帮助确定病人对具体疾病或病症的易感性。在一些实施方案中，个性化用药是综合性的方法，其在药物和诊断的发现和发展的所有阶段利用患者和健康个体的分子分析来指导决定；通过改善的预防、诊断、治疗和监控方法将这种临床实践的知识应用于更有效地提供准确而高质量的医疗保健。

在一些实施方案中，可以以在动物或人类的雌性升值周期中有效调节能育性的量给药式(I)的化合物，或者在一些实施方案中，以有效控制人类月经周期不规律或有效同步或抑制商品化动物（例如鱼、牛、绵羊、猪、山羊或鸡）、实验室动物（例如猿、黑猩猩、大鼠、小鼠或豚鼠）或家养动物（狗、猫、雪貂、兔或马）的生育期的量给药式(I)的化合物。在一些实施方案中，可以以有效减少月经的量给药式(I)的化合物，由此用于治疗或预防贫血和痛经。在一些实施方案中，可以以有效预防或治疗经前期综合征、子宫内膜异位症、平滑肌瘤（子宫肌瘤）和/或卵巢囊肿的量给药式(I)的化合物。而且，对于患有或以前患有盆腔炎性疾病的个体（其中可能已发生输卵管瘢痕形成），可以使用式(I)的化合物以减少可能发生输卵管妊娠的几率。

在一些实施方案中，可以以有效预防妊娠的量给药式(I)的化合物。在一些实施方案中，这种给药可以在排卵前或性交前、或者在排卵后或性交后。在一些实施方案中，这种给药抑制个体的胚胎植入，或在一些实施方案中抑制个体排卵。

在一些实施方案中，可以以有效诱导雌性宫颈成熟的量给药式(I)的化合物。所述宫颈成熟可以是阵痛和分娩后代的准备、或是刮宫术的准备。在另一个实施方案中，实施这种给药以诱导胚胎或胎儿从个体娩出。

应理解，任何本文所述的化合物的任何用途都可以用于治疗本文所述任何疾病、障碍或病症，而且代表本发明的实施方案。

以下所示的实施例是为了更全面地说明本发明的优选实施方案。但是，它们无论如何都不应该被解释为限制本发明的广泛范围。

实施例

实施例 1

I

化合物 XIII 的合成

2-取代丙烯酸（化合物 46）与 4-氰基-3-三氟甲基苯胺反应，然后进行环氧化。在碳酸钾存在下用对-CN-苯酚使环氧化物开环，产生化合物 XIII，如图 1B 中所示。

实施例 2

化合物 V 的合成

4-氰基-3-三氟甲基苯胺与丙烯-2-磺酰氯（51）反应，进行环氧化，然后在碳酸钾存在下用 p-CN-苯酚使环氧化物开环，产生化合物 V，如图 1C 中所示。

实施例 3

化合物 XI 的合成

用 p-CN-苯酚使环氧乙烷基甲基氨基甲酸叔丁酯（54）开环，得到化合物 55 ，然后用 TFA 脱保护，得到氨基醇 56。将化合物 56 引入与 4-氟-2-三氟甲基苄腈的亲电取代反应中，形成化合物 58。将 58 氧化成相应的羰基衍生物 59，将 59 用于进一步的加成反应，得到化合物 XI，其如图 1D 中所示。

实施例 4

化合物 XXXV 的合成

由起始化合物 3,6-二氧杂-双环[3.1.0]己烷（60）制备 4-亚甲基-四氢呋喃-3-醇（61），如图 1E 显示。该化合物用于与 p-CN-苯酚（50）进行 Mitsunobu 型反应，形成化合物 62。用 OsO_4 进行二羟基化，然后在 TEMPO 基(2,2,6,6-四甲基哌啶哌啶基氧)的存在下用 $NaClO_4$ 进行氧化，形成酸 64。使用亚硫酰二氯和 4-氰基-3-三氟甲基苯胺由化合物 64 产生化合物 XXI，如图 1E 中所示。

实施例 5

化合物 XXXVI 的合成

如实施例 4 中所述制备化合物 62，然后进行环氧化，得到化合物 65，如图 1F 中所示。用 4-CN-3-三氟甲基苯胺使环氧化物开环，产生化合物 XXXVI，如图 1F 中所示。

实施例 6

化合物 XLVI 的合成

4-氰基-3-三氟甲基苯胺与衣康酸酐（66）反应，得到中间体 67。进一步环氧化并用对-CN-苯酚使环氧化物开环，产生化合物 XLVI，如图 1G 中所示。

实施例 7

化合物 XLIII 的合成（图 2）

通过肖登-包曼二氏反应使吡咯烷-2-羧酸（56）酰化，得到异丁烯酰基吡咯烷-2-羧酸（57），随后在 *N*-溴丁二酰亚胺的存在下，将其内酯化，得到溴内酯（58）。在回流条件下，用 24% HBr 溶液将所述溴内酯（58）水解 1 h，随后进行后处理并在乙酸乙酯-己烷混合物中重结晶，得到高收率的 3-溴-2-羟基-2-甲基丙酸（59）[59：白色固体（收率：85%）Mp. 108°C $[\alpha]_D^{25}$ = +10.5 (c=2.5,10 MeOH) NMR (^{1}H, 300MHz, DMSO): 1.35 (s, 3H, CH_3), 3.5 (s, 1H, CH), 3.6 (s, 1H, CH), 4.0 (br, 1H, OH) MS: 205 ($M + Na^+$) $C_4H_7BrO_3$ 已计算出: C, 26.25; H, 3.86 发现: C, 26.28; H, 3.75]。

然后，通过在氩气氛下冷却至 0℃，用三溴乙醛保护化合物 59 的羟基和羧基，在搅拌下滴加浓硫酸。2h 后溶液变暗；移去冰浴，反应混合物在室温下搅拌过夜。溶液用冰稀释并用乙酸乙酯萃取，无水硫酸钠干燥并浓缩，得到化合物 60，从乙酸乙酯-己烷中重结晶后，该化合物的外观为白色晶体。[60: 白色固体（收率：89%） Mp. 97°C NMR (^{1}H, 300MHz, $CDCl_3$): 1.8 (s, 3H, CH_3), 3.7 (s, 2H, CH_2), 5.8 (s, 1H, CH) $C_6H_6Br_4O_3$ 已计算出: C, 16.17; H, 1.36;发现: C, 16.08; H, 1.25]。

将化合物 60 溶解在 1:1 的 2-丙醇与 1M NaOH 的混合物中并在室温下搅拌。3h 后，当通过 TLC 检测不到原料时，加入 4'-氟苯硫酚，反应混合物搅拌过夜。然后，用浓 HCl 将反应混合物调节至 pH 1，用乙酸乙酯萃取并用无水硫酸钠干燥。浓缩有机层，得到油。在己烷-乙酸乙酯-乙酸混合物中对反应混合物进行快速柱层析，然后在乙酸乙酯-己烷中进行重结晶，得到无色针状晶体。通过用浓 HCl 酸化反应混合物使该化合物水解以除去保护基，得到图 2 中所示的手性羟酸（55）[55：白色固体（收率：65%） M.p. 54℃; $[\alpha]_D^{25}$ = +24.85 (c=1.0, MeOH) NMR (^{1}H, 300MHz, $CDCl_3$):1.5 (s, 3H,

CH_3), 3.2 (d, 1H, CH), 3.4 (d, H, CH), 7.0 (m, 2H, Ar, J = 2.0 Hz, 8.9 Hz), 7.5 (m, 2H, Ar, J = 2.0 Hz, 8.9 Hz) MS: 无母离子峰 $C_{10}H_{11}FO_3S$，已计算出：C, 52.16; H, 4.82; 发现: C, 52.05.59; H, 4.76]。

通过于 0℃在氯仿介质中加入硫光气和碳酸氢钠，然后在室温下搅拌过夜，将 4-硝基-3-三氟甲基苯胺转化为相应的异硫氰酸盐（66）。浓缩反应混合物，将其萃取至乙酸乙酯中，干燥，蒸发，通过使用己烷-乙酸乙酯混合物的快速柱层析进行纯化，得到外观为黄色固体的 66。在搅拌下加入羟酸 55 和 4-硝基-3-三氟甲基苯基异硫氰酸盐（66）、三氟乙酸银乙腈溶液和三乙胺，反应混合物加热至回流，保持 1h。通过过滤除去硫化银，减压蒸去溶剂，所得剩余物用水洗涤，萃取至乙酸乙酯中，干燥、过滤并浓缩。通过使用己烷-乙酸乙酯混合物的快速柱层析进行分离，所期望的产物呈现为黄色油。鉴定该化合物是噁唑烷二酮（65），如图 2 中所示。[65: 黄色油(收率： 52%)$[\alpha]_D^{25}$ = +39.7 (c=2.5,10 甲醇) NMR (^{1}H, 500MHz, DMSO): 1.8 (s, 3H, CH_3), 3.2 (s, 1H, 20 CH), 3.3 (s, 1H, CH), 6.9 (m, 2H, Ar, J = 2.0 Hz, 8.9 Hz), 7.2 (m, 2H, Ar, J = 2.0 Hz, 8.9 Hz), 7.9 (m, 1H, Ar, J = 2.1 Hz, 9.0Hz), 8.0 (m, 1H, Ar, J = 0.5Hz, 2.1 Hz) 8.1 (m, 1H, Ar, J = 0.5Hz, 9.0Hz) NMR (^{13}C, 500MHz, CDCl3): 22.8, 43.4, 86.7, 117.0, 117.3, 124.4, 124.5, 124.6, 125.0, 126.8, 129.3, 134.2, 134.3, 135.3, 164.9, 172.8 MS: 无母离子峰 $C_{10}H_{11}FO_3S$，已计算出：C, 48.65; H, 2.72; N, 6.30 发现: C, 48.59; H, 2.70; N, 6.31]。

该产物（65）在π受体/供体(R,R)-Whelk-O1 手性柱上的 HPLC 分析显示比率为 70:30 两个峰，对应两个对映异构体，对映异构体过量值为 40%。噁唑烷二酮形成的发生必定经过羟基从亚胺碳上亲核置换硫化银及随后的协同环重排，这可由中间结构（67a）和（67b）得到证实；与 Shibuya 等人建立的机制相同的机制。本文考虑，在上述分析型手性柱中获得的对映异构体的良好分离情况可以扩展至相应的制备柱，以便获得所述对映异构体的定量收率，由此用激子偶联振动圆二色性（exciton coupled vibrational circular dichroism）测定它们的绝对构型，并用以高斯经验计算法辅助测定红外光谱。本文还考虑，杂环体系的氧原子可以用氨基代换以得到对映性的比卡鲁胺的乙内酰脲类似物，然后所述类似物会为与受体的氢键合相互

作用提供额外的位点。

实施例 8

化合物 XLVIII 的合成（图 3）

通过重氮化由 4-氰基-3-三氟甲基苯胺制备 4-溴-2-三氟甲基苄腈（74）。使 4-溴-2-三氟甲基苄腈（74）与 BuLi 反应生成 Li 的衍生物（75）。使 3-溴苄腈与 BuLi 反应生成 Li 的衍生物（77）。用(2-溴乙氧基）-叔丁基二甲基硅烷（78）将 Li 衍生物（77）烷基化，得到衍生物（79），79 用 MeMgI 转化为苯乙酮（80）。随后，脱保护并与对-CN-苯酚发生 Mitsunobu 反应，形成苯乙酮（82）。加入 Li 衍生物（75），然后脱水，得到化合物 XLVIII，如图 3 中所示。

实施例 9

化合物 XLIX 的合成（图 4）

将 4-(2-羟基乙基)-吡啶-2-腈（83）用叔丁基二甲基硅烷保护，并用 MeMgI 将其转化为相应的苯乙酮（85），然后脱保护，制备醚（87）。加入 Li 衍生物（75），然后脱水，得到化合物 XLIX，如图 4 中所示。

实施例 10

化合物 L 的合成（图 6）

通过 4-氯甲氧基苄腈（97）由对-CN-苯酚（50）制备正膦（98），在维蒂希反应中 98 与 3-乙酰基苯甲醛（99）生成衍生物（100）。随后，加入如实施例 8 中所述的 Li 衍生物（75），然后脱水，得到化合物 L，如图 6 中所示。

实施例 11

化合物 LI 的合成（图 7）

用叔丁基二甲基硅烷保护 3-羟甲基苄腈（101），得到化合物（102），随后用 MeMgI 得到相应的苯乙酮（85）。除去保护基，进一步与对-CN-苯酚反应以得到（105）。向（105）中加入 Li 衍生物（75）（如实施例 8 中所

制备），然后脱水，得到化合物 LI，如图 7 中所示。

实施例 12

化合物 LII 的合成（图 5）

用叔丁基二甲基硅烷保护 5-溴-2-羟基苄腈（88），得到化合物（89）。化合物（89）与 BuLi 反应，得到 Li 衍生物（90），其进一步由(2-溴乙氧基)-叔丁基二甲基硅烷烷基化，得到（91）。化合物（91）与 MeMgI 反应成相应的苯乙酮（92），然后脱保护并选择性地保护酚基，得到衍生物（94）。衍生物（94）与对-CN-苯酚反应，得到化合物（95），然后加入 Li 衍生物（75）并脱水（如实施例 8 中所述），得到化合物（96）。随后脱保护，得到化合物 LII，如图 5 中所示。

实施例 13

化合物 XXIV 的一般合成（图 1I）

根据图 1I 制备 4-(4-芳基磺酰-2,5-二甲基哌嗪-1-基)-2-三氟甲基苄腈。于 DMSO-水混合物中在碳酸钾存在下，用 2,5-二甲基哌嗪亲核取代 4-氟-2-三氟甲基苄腈中的氟原子。在三乙胺存在下，通过与芳基磺酰氯的反应制备相应的芳基磺酰衍生物。

实施例 14

雄激素受体（AR）与 SARM 的结合以及 AR-SARM 晶体结构

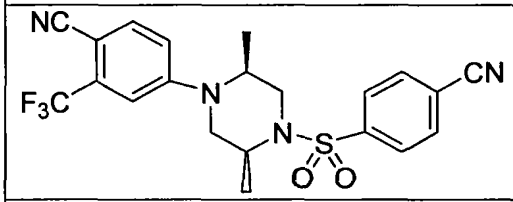
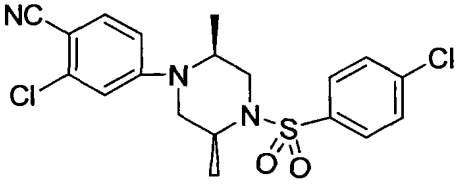
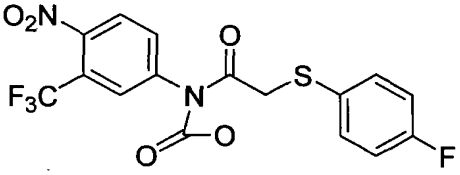
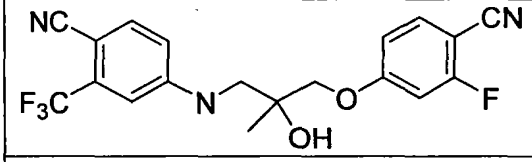
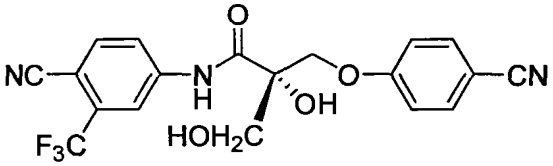
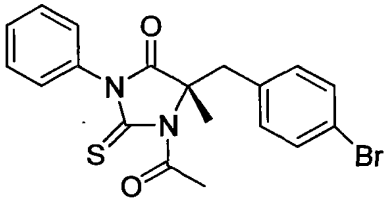
方法

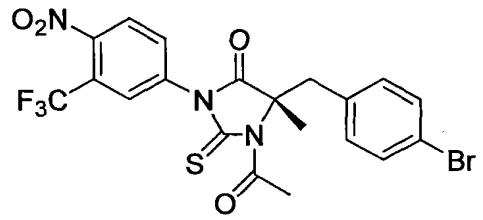
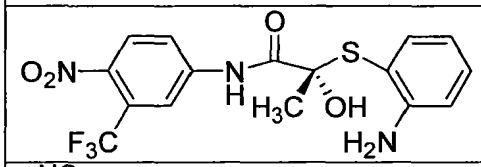
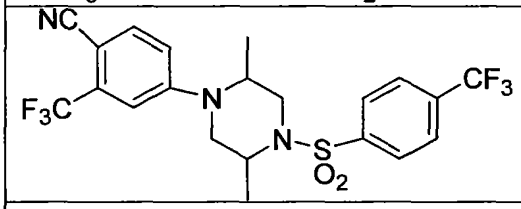
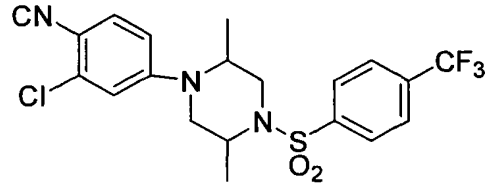
亲合力测定

由斯普拉-道来(氏)大鼠的腹部前列腺得到细胞溶胶 AR。切除前列腺并立即浸没在冰冷的匀浆缓冲液中（10 mM Tris、1.5 m MEDTA 二钠、0.25 M 蔗糖、10 mM 钼酸钠和 1 mM PMSF）。用剪刀将前列腺切碎，匀浆并离心（Model L8-M，Beckman Instruments Inc）。收集上清液（细胞溶胶）并储存在-80℃下直到使用。在存在或不存在浓度增加的感兴趣的化合物（10^{-1} nM-10^{4} nM）的情况下，于 4℃下用饱和浓度的 ^{3}H-MIB (1 nM)和 1 μM 的曲安奈德培养等份（50 μL）的 AR 细胞溶质 18 h。

通过向培养液中加入 1000 nM MIB，测定 ^{3}H-MIB 的非特异性结合。使用羟基磷灰石分离结合的和游离的放射性配体并测定结合的 ^{3}H-MIB 的浓度。使用非线性回归测定 IC_{50}，即抑制 50% ^{3}H-MIB 的特异性结合的供试化合物的浓度。

测定本发明的化合物的亲合力并显示在下表中：

化合物	抑制常数（nM）
	633.5
	528.9 nM
	195.81 nM
	412.24 nM
	396.8 nM
	微摩尔范围

	微摩尔范围
	70.7 nM
	2785 nM
	2632 nM

共转染测定

使 CV-1 细胞（绿猴肾细胞）在补充了 10% FBS、2mM 谷氨酰胺和 1% 链霉素和青霉素的达尔伯克氏改良伊格尔氏培养基（DMEM）上生长到在 T175 组织培养烧瓶中融合。无血清 DMEM 中，将细胞用 3 μg CMVhAR 表达载体、30 μg 雄激素依赖型萤光素酶报道基因构建体(pMMTV-luc)和 30 μg β-半乳糖苷酶表达构建体（pSV-β-半乳糖苷酶；Promega, 5 Madison, WI）经 30 mLPlus 试剂（Invitrogen）和 40 mL LipofectAMINE（Invitrogen）转染。4 小时后，将培养基换成补充 0.2 % FBS 和 2 mM 谷氨酰胺的 DMEM。12 小时后，将细胞转移至 24 孔组织培养板，再过 6 小时后，用 0.1 nM-1000 nM 的药物或不加药物（对照）处理。另外 24 小时后，细胞用冷 PBS 洗涤两次，通过用 100 ML 的被动性溶胞解缓冲液（Promega）培养 30 分钟后收集细胞。

将等份（50 ML）溶胞产物加到不透明的 96 孔板，在自动注入 50 mL 萤光素酶底物（Promega）后，用 MicroLumatPlus LB96V 发光计（Berthold Technologies, Oak Ridge, TN）使用 WinGlow 软件包监测萤光素酶的活性。另将等份（50 mL）的溶胞产物和 50 mL β-半乳糖苷酶测定缓冲液一起加到

透明的96孔板。在37℃下培养2小时后，在Dynex MRX读板器上于420 nm测定吸收值。使萤光素酶活性与 β-半乳糖苷酶活性标准化，以便计算细胞数量和/或转染率损失的差异。

克隆、表达和纯化

由全长AR表达构建体（pCMVhAR）通过用含有侧翼限制酶切位点的引物进行PCR扩增获得AR-LBD（663-919），然后将其插入到pGEX6P-1质粒载体（Amersham）中。通过用30μM IPTG诱导，所述AR LBD于15℃下在大肠杆菌BL21 DE3中表达16小时，为谷胱甘肽-S-转移酶（GST）融合蛋白。在含有150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10% 甘油、1 mg/mL 溶菌酶、10 U/mLDNA酶I、10 mM $MgCl_2$、10 mM DTT、0.5% CHAPS、100 μM配体和100 μM PMSF的缓冲液中，通过三次冻融循环，将细胞溶解。由超速离心得到的上清液与谷胱甘肽琼脂糖凝胶（Amersham）在4℃下培养1 h，并用150 mM NaCl、50 mM Tris pH 8.0、5 mM EDTA、10%甘油、10 mM ATP、10 DM配体、0.1% *n*-辛基-β-葡糖苷和1 mM DTT洗涤。

于4℃下在含有150 mM NaCl、50 mM Tris pH 7.0、10%甘油、0.1% *n*-辛基-β-葡糖苷、1 mM DTT和5 U/mg蛋白质PreScission蛋白酶（Amersham）的缓冲液中过夜切割GST-LBD融合蛋白以从谷胱甘肽琼脂糖凝胶中释放AR LBD。上清液在10 mM pH 7.2的羟乙基哌嗪乙磺酸、10%甘油、10 μM配体、0.1% *n*-辛基-β-葡糖苷、1 mM DTT中稀释3倍，然后装载至HP SP阳离子交换柱（Amersham）上。在相同的稀释缓冲液中用50 mM-500 mM的 NaCl梯度洗脱蛋白。在Millipore 10 kD截留浓缩器中将缓冲液换成含有150 mM Li_2SO_4, 50 mM pH 7.2的羟乙基哌嗪乙磺酸、10%甘油、100 μM配体、0.1% *n*-辛基-β-葡糖苷和10 mM DTT的缓冲液，将蛋白质浓缩至大于4 mg/mL。

结晶、收集数据和结构测定

在一至两天内，利用悬滴蒸发扩散法于0.1 M pH 7.5羟乙基哌嗪乙磺酸和0.5 M-0.8 M的柠檬酸钠中形成 AR LBD晶体。在液氮中快速冷冻之前，将AR LBD晶体转移至由0.1 M pH 7.5的羟乙基哌嗪乙磺酸、0.7 M柠檬酸钠和20%乙二醇组成的溶液中。使用Rigaku RU300旋转阳极发生器

和 R-轴 IV++成像板（Rigaku）收集衍射数据，并用 Crystal Clear 软件进行处理（Molecular Structure Corporation）。AR LBD-DHT 复合物（PDB 编码 1I37）用作使用 Crystallography & NMR System（CNS）进行精制的起始结构。在第一轮精制后，电子密度图使配体准确拟合（fitting）。使用程序 O 加入模型构建物和水分子，使用刚性体、扭转角模拟重结晶法和 CNS 的单个温度因子模块进行更多轮的精制。

SARM 的 X 射线研究

将显示 AR 结合低于 100 nM 的 SARM 在萤光素酶测定中进一步分析，以确定它们是否具有 AR 功能性激动剂活性。随后，使具有最高活性的 SARM 与 AR 受体共结晶并进行 X 射线分析。

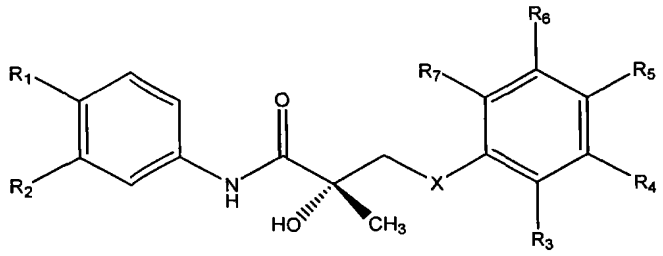
实施例 15

SARM 的功能活性

表 1 描述了所示醚连接化合物（比卡鲁胺类似物）的结构和亲合性。所有化合物都使用手性合成方法合成，包括使用 D-脯氨酸作为手性助剂，如美国专利 6,995,284 中所公开地，该专利通过引用结合于此。使用元素分析和波谱数据，即 ^{1}H NMR、^{13}C NMR、MS 和 IRE 确定合成的化合物的结构。

在本发明的一些方面，这些化合物的设计充分理解被鉴定为涉及比卡鲁胺类似物的 AR 亲合力的结构元素，例如：(i) 缺电子的芳香性 A 环，(ii) 在手性中心的 *R*-构型，和(iii) 在 B 环的对位的亲电子基团。重要的是要注意，在这类分子中，当用醚键代替硫醚或磺酰基连接时，活性化合物的手性指示从*(R)*变为*(S)*。除了这些对高 AR 结合亲合力所需的结构特征外，B 环取代和连接基 X 的性质是比卡鲁胺类似物的功能活性的关键性决定因素。

表 1：



编号	R1	R2	X	R3	R4	R5	R6	R7	K_i (nM)
比卡鲁胺	CN	CF_3	SO_2	H	H	F	H	H	11±2
R-20	NO_2	CF_3	SO_2	H	H	COCH3	H	H	9.3±0.8
S-1	NO_2	CF_3	O	H	H	F	H	H	6.1±0.19
S-2	NO_2	CF_3	O	H	H	COCH3	H	H	36.6±2.3
S-3	NO_2	CF_3	O	H	H	$COCH_2CH_3$	H	H	6.1±0.14
S-4	NO_2	CF_3	O	H	H	NHCOCH3	H	H	4.0±0.70
S-5	NO_2	CF_3	O	H	H	CH_3	H	H	34.8±3.5
S-6	NO_2	CF_3	O	H	H	OCH3	H	H	13.7±0.68
S-7	NO_2	CF_3	O	H	H	$NHCO_2C(CH_3)3$	H	H	336.0±71.1
S-9	NO_2	CF_3	O	H	H	H	H	H	4.6±0.26
S-10	NO_2	CF_3	O	F	H	F	H	H	3.4±0.34
S-11	NO_2	CF_3	O	H	F	F	H	H	3.4±0.56
S-12	NO_2	CF_3	O	F	H	F	H	H	3.2±0.30
S-13	NO_2	CF_3	O	CH3	H	F	H	H	6.0±0.70
S-14	NO_2	CF_3	O	H	Cl	F	H	H	10.3±2.0
S-15	NO_2	CF_3	O	H	F	Cl	H	H	4.9±0.3
S-16	NO_2	CF_3	O	H	Cl	Cl	H	H	1.0±0.088
S-17	NO_2	CF_3	O	F	F	F	H	H	11.3±1.1
S-18	NO_2	CF_3	O	F	H	F	H	F	10.3±2.0
S-19	NO_2	CF_3	O	F	F	H	F	H	9.1±0.6
S-20	NO_2	CF_3	O	F	F	F	F	F	1.4±0.34

S-21	NO_2	CF_3	O	H	H	Cl	H	H	8.6±1.2
S-22	NO_2	CF_3	O	H	H	Br	H	H	12.6±1.8
S-23	NO_2	CF_3	O	H	H	I	H	H	22.6±1.6
S-24	NO_2	CF_3	O	H	H	$NHCSNH_2$	H	H	10.2±1.4
S-25	NO_2	CF_3	O	H	H	$NHCSNHCH_3$	H	H	271.2±37.2
S-26	CN	I	O	H	H	F	H	H	3.3±0.10
S-27	CN	CF_3	O	H	H	Cl	H	H	3.4±0.08
S-28	CN	CF_3	O	H	H	$NHCOCH_3$	H	H	12.7±0.02
S-29	CN	Cl	O	H	H	F	H	H	4.5±0.11
S-30	CN	CF_3	O	H	H	F	H	H	3.3±0.08
S-31	F	CF_3	O	H	H	F	H	H	32.6±0.10
S-32	Cl	CF_3	O	H	H	F	H	H	14.5±0.18
S-33	I	CF_3	O	H	H	F	H	H	15.6±0.19
S-34	Br	CF_3	O	H	H	Cl	H	H	52.0±0.13
S-35	Br	CF_3	O	H	H	Br	H	H	25.9±0.04
S-36	H	CF_3	O	H	H	F	H	H	62.0±0.05

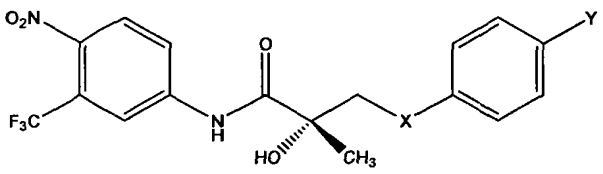
对 AR 介导的转录激活的体外研究（图 8）显示，将 X 连接由砜变为氧或将 B 环对位取代由氟变为乙酰胺基都将纯粹的 AR 拮抗剂转化为激动剂，例如在化合物 S-5 和 R-20 中。在体内试验中，先导化合物 S-1 和 S-4 在体内用作 AR 激动剂并显示出组织选择性（图 9A-9B)。S-1 和 S-4 在前列腺中都是部分激动剂，但是在肛提肌、骨和垂体中是完全激动剂，这些是对理想的选择性雄激素受体调节剂提出的特征。

S-4 的口服生物利用度和安全性已经被证实（数据未显示），确证了这些化合物可能有效治疗雄激素缺乏性疾病或病症的观点。先前已经证明，S-1 和 S-4 不是 5α-还原酶的底物。本文考虑，这些配体的组织选择性是因

为它们在前列腺中的激动剂活性没有完全被 5α-还原酶放大，5α-还原酶是在前列腺中而不是肌肉中表达的、将睾酮转化为 DHT 的酶。

表2显示最大疗效百分数对表1的各种化合物的X-和Y-位置的依赖性。如实施例 13 中所述，使用大鼠腹部细胞溶胶作为 AR 源，利用竞争性结合测定来测定完整 AR 的亲合力。如实施例 13 中所述，使用共转染测定，检测完整 AR 的体外功能活性。在 10 nM 配体下分析疗力（即转录激活），将活性表示为对 1 nM 双氢睾酮（DHT）观察到的最大转录激活的百分数。

表 2



ID	X	Y	亲合力 (nM)	疗效 (%最大)
S-1	O	F	6.11 ± 0.19	43.40 ± 2.60
X-2	S	F	11 ± 2	77.4 ± 5.6
X-3	SO_2	F	28 ± 10	18.8 ± 9.3
X-4	NH	F	7.96 ± 0.43	21.33 ± 2.22
X-5	CH_2	F	9 ± 0.2	28.9 ± 2.4
S-4	O	$NH(CO)CH_3$	3.98 ± 0.70	92.92 ± 7.00
S-23	O	I	23 ± 1.6	47.2 ± 1.8

实施例 16

非类固醇配体结合的结构表征

对一系列 4”-氟苯基-2-羟基-2-甲基-*N*-(4’-硝基-3’-三氟甲基苯基)丙酰苯胺化合物进行构象分析，这些化合物仅 X 位置的杂原子不同。该分析检

测了 X 位置取代基对溶液中化合物构象的影响以开发构象化合物。将配体溶液（DMSO-d_6）NMR 构象与它们的来自新近解析的 *R*-比卡鲁胺-W74L-LBD 晶体结构（本文中称为比卡鲁胺-W741L；C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc Natl Acad Sci U S A* **2005**, *102(17)*, 6201-6. ）的结合构象作比较。已经预料在连接部位中的分子内氢的键合（NH-OH），这在溶液构象中观察到了。然而，对于一些被分析的化合物，这种分子内 NH 氢键供予在 OH 和 X 位置间共享。NH-X 氢键导致所述配体在溶液中的总体形状获得意想不到的弯曲，这种弯曲与在 AR 的同源建模过程中得到的假设性的结合构象明显不同。过去，对丙酰苯胺没有六元 5 环状 NH-X 氢键合构象的假设。激动剂 S-4(X=O,Y=N-乙酰基)和 X-2(X=S,Y=F)和部分激动剂 S-23(X=O,Y=I)和 S-1(X=O,Y=F)最清楚地显示出这种溶液中苯环的 NH 至-X 加-OH 构象（图 10），但是，对于该系列的拮抗剂 X-3(X=SO_2, Y=F)和 X-4(X=NH, Y=F)和 X-5(X=CH_2 ,Y= F)没有观察到这种构象。这表明，所述配体采取这种构象的能力可能对 AR 激活很重要，这一点通过与非类固醇配体的构象的比较得到确证，所述非类固醇配体的构象是在随后解析的 *R*-比卡鲁胺-W741L-LBD（AR 突变体，其中比卡鲁胺用作激动剂）的 X 射线晶体结构中观察到的。

表 3 提供表 1 所中所鉴定的各种化合物的溶液中分子内氢键分析的结果。如表 3 中使用的，氢键的定义是<3.1Å 的原子间距离，该距离是在 SYBYL 6.8 中使用分析->>距离命令测得的。

溶液构象使用 NOESY 谱测定。NH-OH 指连接部位酰胺的质子和连接部位羟基的氧之间的原子间距离，NH-X 指连接部位酰胺的质子和连接部位 X 位置的原子之间的原子间距离。S-1 在体外用作部分激动剂，S-4 和 X-2 在体外是激动剂，X-3、X-4 和 X-5 在体外是拮抗剂。

表 3：

ID	NH-OH	NH-X
S-1	2.4	2.3
S-4	2.7	1.9

X-2	2.1	3.0
X-3	2.0	3.6
X-4	2.3	4.4
X-5	2.0	3.9

构建 AR 的位点特异性突变体，检测 DHT 和三种非类固醇配体即羟基氟他胺（HF）、比卡鲁胺和 S-4 刺激 AR 介导的转录的能力（图 11）。在该突变体中，比卡鲁胺表现为激动剂并刺激 AR 介导的转录激活，表明结合比卡鲁胺的 W741L 突变体 AR-LBD 采取类似于用结合激动剂的野生型 AR 观察到的构象的活性构象。考虑到纯化结合拮抗剂的野生型 LBD 的困难，结合比卡鲁胺的 W741L 突变体和结合羟基氟他胺的 T877A 突变体的激动剂构象证明是有用的。本文考虑，这些突变体复合物会采取更紧凑的构象，这样会促进在 LBD 的纯化和结晶过程中伴侣蛋白质的解离，并为我们提供对非类固醇 AR 配体结合机制的首次了解。

使用类似于首先解析与类固醇配体结合的 AR-LBD 晶体结构的科学家所述的方法，将结合 R1881 和 DHT、DHT-5 的野生型 LBD 和结合比卡鲁胺的 W741L LBD 纯化并结晶。而且，使用亲合力更高的比卡鲁胺 *R*-异构体。在大肠杆菌中，GST-LBD 与配体共同表达。在亲和层析和裂解融合蛋白后，LBD 的高 pI（等电点）使杂质蛋白和伴侣蛋白质通过中性 pH 阳离子交换色谱除去。

这两种复合物均采取与结合类固醇的 LBD 非常类似的整体构象（图 12A）。如由溶液构象的 NMR 研究所预示的，比卡鲁胺在磺酰基氧和胺类质子之间形成分子内氢键（图 12B），这与计算机预测的模型（图 10）不同，指示这是不同于醚连接类似物的构象，并表明对配体溶液构象的 NMR 研究可能用于预测与 LBD 结合时的配体构象。这种结象说明，这些突变为非类固醇配体提供更多的空间以嵌入（fit into）LBD，并形成由野生型 DHT 复合物观察到的激动剂构象。

大多数 LBD 残基在野生型 DHT 复合物中的位置类似于非类固醇复合物，尽管配体结构的变化程度惊人（图 13A）。羟基氟他胺（HF）和 *R*-比卡鲁胺具有类似的 A 环和酰胺键结构，这使类固醇平面完全重叠（图 13B）。

在 R752 和 A 环的硝基/氰基之间观察到氢键，这模拟了 DHT 中的 3-酮基，而且在 L704 和 N705 和羟基之间也观察到氢键，这模拟了 DHT 中的 17β-OH。然而，与 DHT 不同的是，在非类固醇配体和 T877 侧链之间没有观察到氢键。

在 R-比卡鲁胺的砜连接基和 B 环区域也观察到残基的位置有很大区别（图 13B），该区域折叠离开类固醇平面并指向口袋（pocket）的顶部，可能占用 W741 吲哚环(在突变体中不存在)的空间。在 T877A-HF 和 WT-DHT 复合物中，W741 吲哚环的位置也区别很大。在 DHT 复合物中，Trp741 侧链与配体接触，而在 T877A-HF 复合物中，该吲哚环距离结合口袋（binding pocket）更远。M745 由 DHT 的 19-甲基置换似乎能解释这些区别。在图 13B 中也看到，与野生型 DHT 和 T877A-HF 相比，*R*-比卡鲁胺磺酰基造成螺旋 12 残基 M895 的置换。然而，该 M895 侧链被容纳在 T877A-HF 复合物的 W741 吲哚环的位置中。在野生型 LBD 中，W741 和 M895 侧链都可能与比卡鲁胺具有不利的阻止激动剂构象形成的相互作用。另一方面，R-比卡鲁胺的 B 环对位上的氟在 AR 的亲水区域结合，所述区域也提供形成氢键的机会。AR 的这一区域位于螺旋 4 和 5 之间的扭转处并与 H874 咪唑十分接近。在该位置被乙酰胺基 S-4、异硫氰酸盐、氰基或硝基取代的化合物证明对 AR 具有改善的亲合力，表明在该区域它们可能形成有利的氢键。

实施例 17

结合激动剂和拮抗剂的 AR LBD 的结构特征

HSP 的解离是由激动剂诱导的 AR LBD 构象变化引起的初始过程之一。在哺乳动物细胞中，HSP 复合物主要包含 HSP90、HSP70、p60 和 p23。HSP90 直接与受体结合成为同型二聚体，而其它蛋白质主要通过 HSP90 与该复合物结合。AR LBD 中的 HSP90 结合位点还没有被很好地表征。包括环 3-4、H4 和 H5 的残基 720-774 正好形成大部分的 AF2 疏水性凹槽（图 14A-14B），它们被鉴定为可能负责使用截短的结合 HSP90 的区域。

重要地，本文考虑，异常的曝露于溶剂的 HSP90 的 α-螺旋与细胞核受体家族的 H12 非常类似，并可能置换这些受体上的 H12 以促进配体结合。

这个观点尤其可能与 AR 有关，因为 AR 的功能与其它细胞核受体相比似乎有重要的不同。放射标记的 AR 的 IP 和蔗糖梯度离心分析显示，激动剂 R1881（而不是拮抗剂羟基氟他胺和比卡鲁胺）诱导 HSP90 解离，这说明伴侣蛋白质复合物的存在而不是 H12 的 MAEII 模体阻止接近 AF2 区。因此，HSP90 的解离似乎直接与 AR 配体的活性有关。

虽然羟基氟他胺用作野生型 AR 的拮抗剂，但是它对 T877A AR 突变体起激动剂作用。其对突变的 AR 的激动剂活性直接与 HSP90 的解离有关。这与 ER 完全不同，其中 ER 激动剂和拮抗剂都启动 HSP 的解离。与 ER 的情况相比，HSP90 的解离对 AR LBD 似乎是能影响受体的构象的更关键的因素。这说明 AR 拮抗剂活性可能涉及另一种机制。

不同 AR 复合物的限制性蛋白水解分析表明，AR 的配体诱导的激活需要 LBD 的两次连续的构象变化。AR 激动剂，即 T、DHT 和 R1881，稳定了 AR 的 29-KD 片段对抗限制性胰蛋白酶消化，而抗雄激素，即醋酸环丙孕酮、羟基氟他胺、尼鲁米特和比卡鲁胺稳定 35-KD 片段。29-KDa 和 35-KDa 片段都含有完整的 LBD（氨基酸 671-919），35-KDa 片段延伸进入铰链区（氨基酸 621-671）。35-KDa 片段也参与激动剂结合的初始步骤，但是在长时间的消化作用下其不稳定。

这种时间依赖性构象变化被钼酸盐的加入而延迟，这说明 HSP 的解离可能导致铰链区暴露于胰蛋白酶消化。因此，已经提出，激动剂结合启动 AR 的第一次构象变化，这触发 HSP 的解离，然后开始第二次构象变化。然而，尽管拮抗剂能启动第一次构象变化，但是它不能促进 HSP 的解离，这稳定了 LBD 和铰链区并保护铰链区不受进一步的胰蛋白酶消化。

实施例 18

对 SARM 进行基于结构的药物设计（SBDD）的全新方法

在基于激动剂与 AR 的结合构象来设计激动剂方面，与拮抗剂比卡鲁胺结合的 AR 突变体 W741L（bicW741L）使我们洞悉本文提供的化合物的结合模式。这也为区分激动剂和拮抗剂的结合模式特征提供了原理。最近解析的结合激动剂 S-1 的野生型 AR（S1-野生型）的晶体结构确证了在 W741L 突变体中观察到的结合模式。在 1.8 Å 的清晰度下，这些结构都被

解析，而且这些结构证明了新型的结合模式，该模式根本上不同于在共晶结构出现之前提出的、由同源模型所表明的模式。

与上述共晶相反，同源模型沿所对接的（docked）类固醇的 α-面具有独特的未被占据的空腔，所述空穴大到足够能容纳丙酰苯胺的 B 环。

确认全新 SBDD 模型

通过 Spearman 相关系数分析对这些 AR 结构模型进行的经验分析提供了每一种模型预测配体亲合力的等级次序的能力的统计学手段。当使用基于分子对接的方法例如全新设计或虚拟筛选以评价该模型是否能用于按优先次序确定应该沿着哪些经计算机模拟（*in silico*）的指导进行时，这种等级顺序统计量是适当的。将为比较分子场分析（CoMFA）模型而编辑的 AR 配体数据库用于以下 AR 模型的 Spearman 分析：CoMFA、结合 S-1 的野生型晶体（简称为 S1-野生型），结合比卡鲁胺的 W741L 晶体（简称为比卡鲁胺 c-W741L）和同源模型。CoMFA (C. E. Bohl, C. Chang, M. L. Mohler, J. Chen, D. D. Miller, P. W. Swaan, J. T. Dalton. A ligand-based approach to identify quantitative structure-activity relationships for the androgen receptor. J Med Chem 2004, 47(15), 3765-76.)、S1-野生型(C. E. Bohl, D. D. Miller, J. Chen, C. E. Bell, J. T. Dalton. Structural basis for accommodation of nonsteroidal ligands in the androgen receptor. J Biol Chem 2005, 280(45), 37747-54.)、比卡鲁胺-W741L (C. E. Bohl, W. Gao, D. D. Miller, C. E. Bell, J. T. Dalton. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. Proc Natl Acad Sci U S A 2005, 102(17), 6201-6.)和 G1 同源模型((C. A. Marhefka, B. M. Moore, 2nd, T. C. Bishop, L. Kirkovsky, A. Mukherjee, J. T. Dalton, D. D. Miller. Homology modeling using multiple molecular dynamics simulations and docking studies of the human androgen receptor ligand binding domain bound to testosterone and nonsteroidal ligands.*J Med Chem* **2001**, *44(11)*, 1729-40.)的 R_s 值分别为 0.93、0.55、0.29 和-0.28，这说明，S1-野生型模型显著的预测值和比卡鲁胺-W741L 模型有限的预测值表明与以前的基于结构的药物设计模型相比有进步。因此，可以预测这些晶体结构能改善确定由计算机模拟的指导的优先次序的能力，由此促进药物设计。

实施例 19

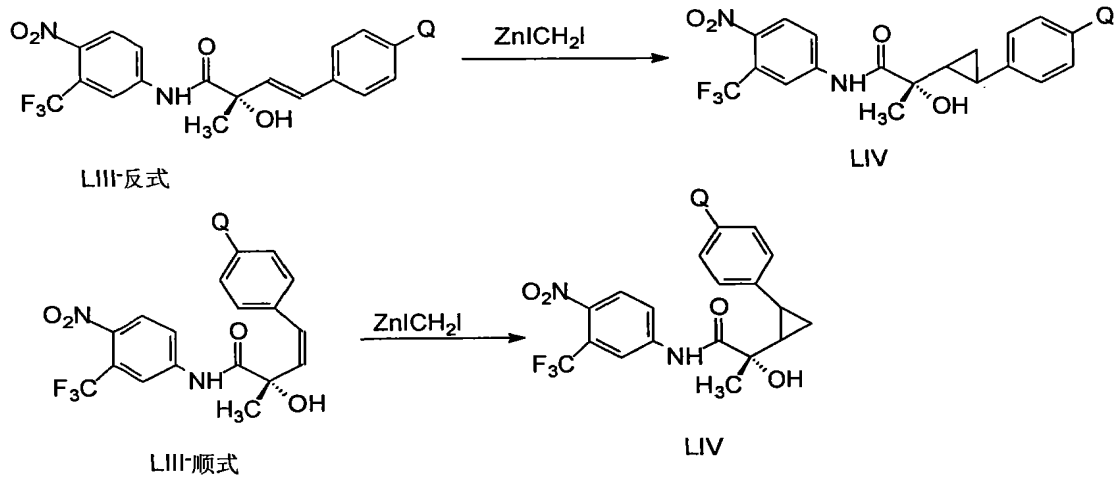
AR 配体结合的计算预测的确认

对实施例 16 中的扭应变参数和氢键相互作用的检验显示，化合物 XVII 的芳基丙酰胺衍生化合物采取类似于化合物 XLII 的构象。羟基 α 以这样的方式定位到羰基，它参与和受体的天冬酰胺 705 的氢键相互作用。该氨基酸与亮氨酸 704 的主链氧形成弱的氢键。所做的计算预测与结合测定得出的结果一致。然而，为了令人信服地建立上述相互作用和分子采取的构象，建立了合适的分子模型，该模型没有自由羟基和酰胺质子，而且最重要的是，该模型在构象上局限于类似于化合物 XLII 的结构。因此，酰胺氮和羟基氧通过羰基官能团连结，这形成如化合物 XXXIX 中所描绘的噁唑烷二酮衍生物结构。实施芳基丙酰胺衍生的化合物的合成和这些噁唑烷二酮衍生物的立体选择性合成。

实施例 20

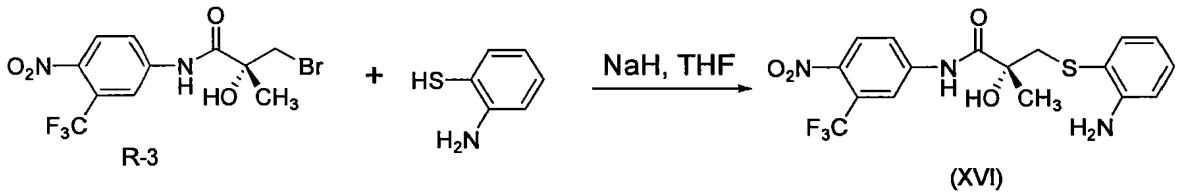
化合物 LIV 的合成

通过化合物 LIII 合成化合物 LIV，所考虑的第一组化合物是通过西蒙斯-史密斯反应合成的环丙烷系列，如以下路线所示。



实施例 21

化合物 XVI 的合成



根据上述路线合成化合物 XVI。根据 US 06995284 合成 R-3，该专利通过引用结合于此。得到 XVI，为黄色油：计算出的质量 415.08, [M-H] 414.0; ^{1}H NMR ($CDCl_3$) 9.13 (bs, 1H, NH), 7.96 (d, J = 9.0 Hz, 2H, ArH), 7.88 (dd, J = 9.0, 2.1 Hz, 1H, ArH), 7.43 (dd, J = 7.6, 1.5 Hz, 1H, ArH), 7.11 (m, 1H, ArH), 6.72 (m, 2H, ArH), 4.15 (bs, 3H, OH & NH2), 3.59 (d, J = 14.1 Hz, 1H, CH2), 3.02 (d, J = 14.1 Hz, 1H, CH2), 1.56 (s, 3H, CH3)。

实施例 22

化合物 XL 的合成

如图 1J 中所描绘地合成化合物 XL。向乙醇中的 L-丙氨酸钠盐中加入异硫氰酸苯酯，温热 30 分钟。蒸去溶剂，并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾盐的存在下加入 1-溴-4-溴甲基苯，得到化合物 XL。

化合物 2 的 ^{1}H NMR ($CDCl_3$)：7.65, 7.63, 7.61, 7.38, 7.35, 7.25, 4.40, 1.62

化合物 3 的 ^{1}H NMR ($CDCl_3$)：7.59, 7.57, 7.56, 7.39, 7.33, 4.92, 2.90, 1.74

化合物 XL 的 ^{1}H NMR ($CDCl_3$)：7.53, 7.52, 7.51, 7.50, 7.49, 7.40, 7.39, 7.37, 7.34, 4,38, 1.67, 1.66；化合物 XL 的熔点：99℃。

实施例 23

化合物 XLI 的合成

如图 1K 中所描绘地合成化合物 XLI。向乙醇中的 L-丙氨酸钠盐中加入 4-异硫氰基-1-硝基-2-三氟甲基苯，温热 30 分钟。蒸去溶剂并向油状剩余物中加入浓 HCl。收集形成的白色固体，在水中洗涤，得到化合物 2。加入乙酸酐，得到化合物 3，在六甲基二硅氮烷钾的存在下加入 1-溴-4-溴甲基苯，得到化合物 XLI。

化合物 3 的 ^{1}H NMR ($CDCl_3$)：10.80, 8.35, 8.18, 7.99, 4.49, 1.43。

化合物 XLI 的 ^{1}H NMR ($CDCl_3$)：7.97, 7.47, 7.43, 7.42, 7.19, 7.15, 6.97,

6.92, 3.93, 3.15, 2.88, 1.98。

虽然本文已经说明和描述了本发明的某些特征，但是本领域的普通技术人员现在会得出许多修改、替换、改变和等同形式。因此，应该理解，所附的权利要求书意在覆盖所有落在本发明的真正精神范围内的这种修改和变化。

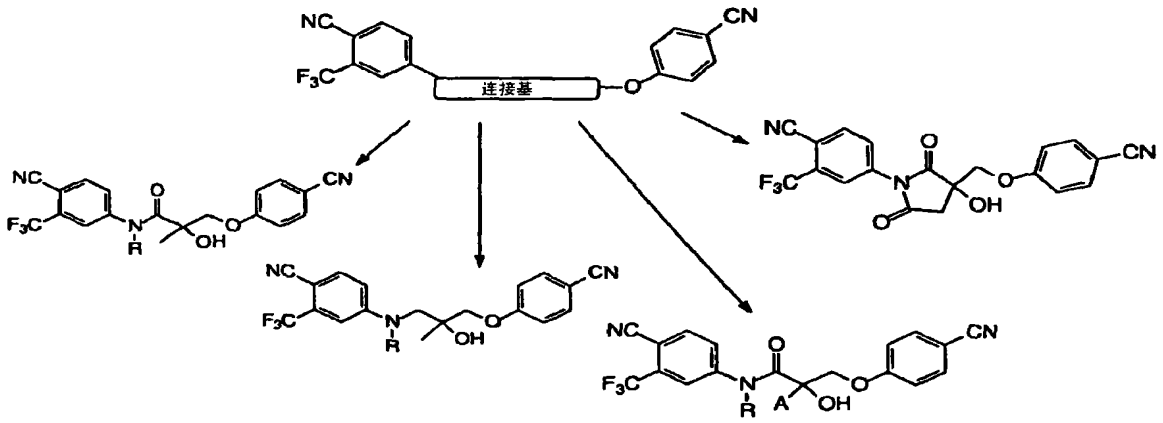

NC
CN
F3C
连接基
O
OH
N
R
A

图1A

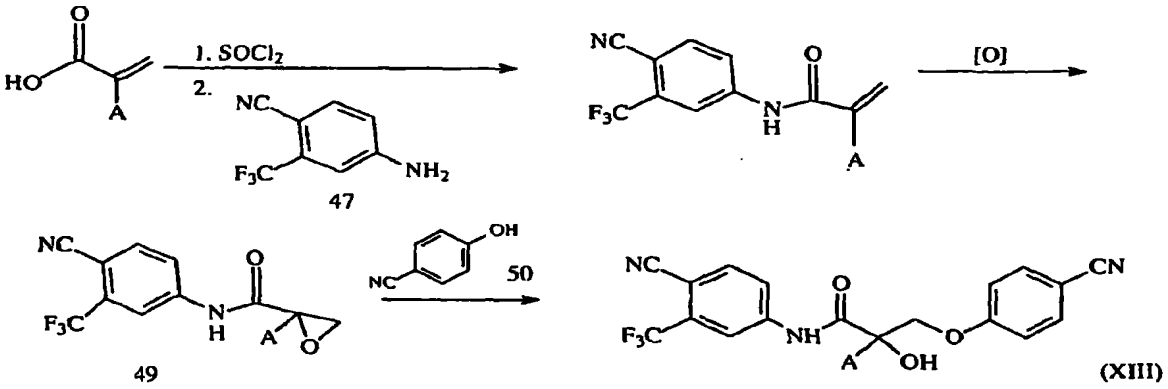

HO
O
A
1. SOCl2
2.
NC
F3C
NH2
47
[O]
N
H
49
50
OH
NH
(XIII)

图1B

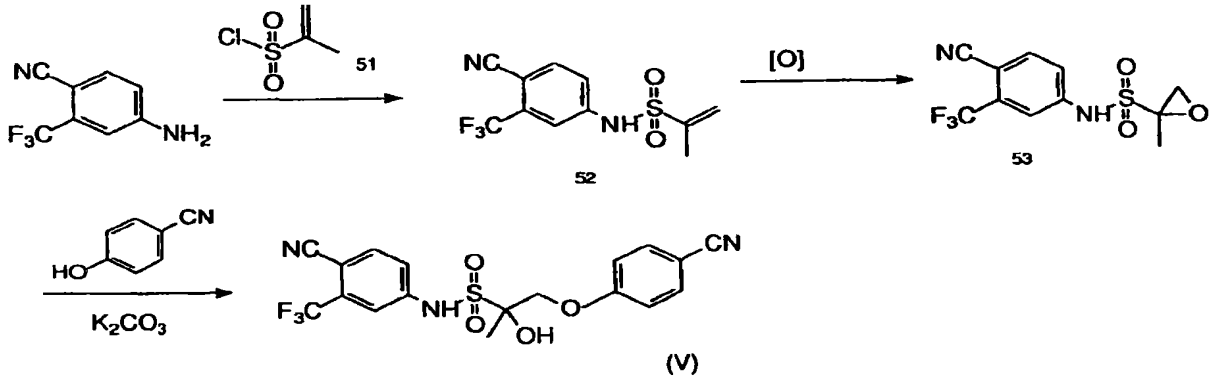

NC
F3C
NH2
Cl
O
S
O
51
52
[O]
53
HO
CN
K2CO3
NH
OH
(V)

图1C

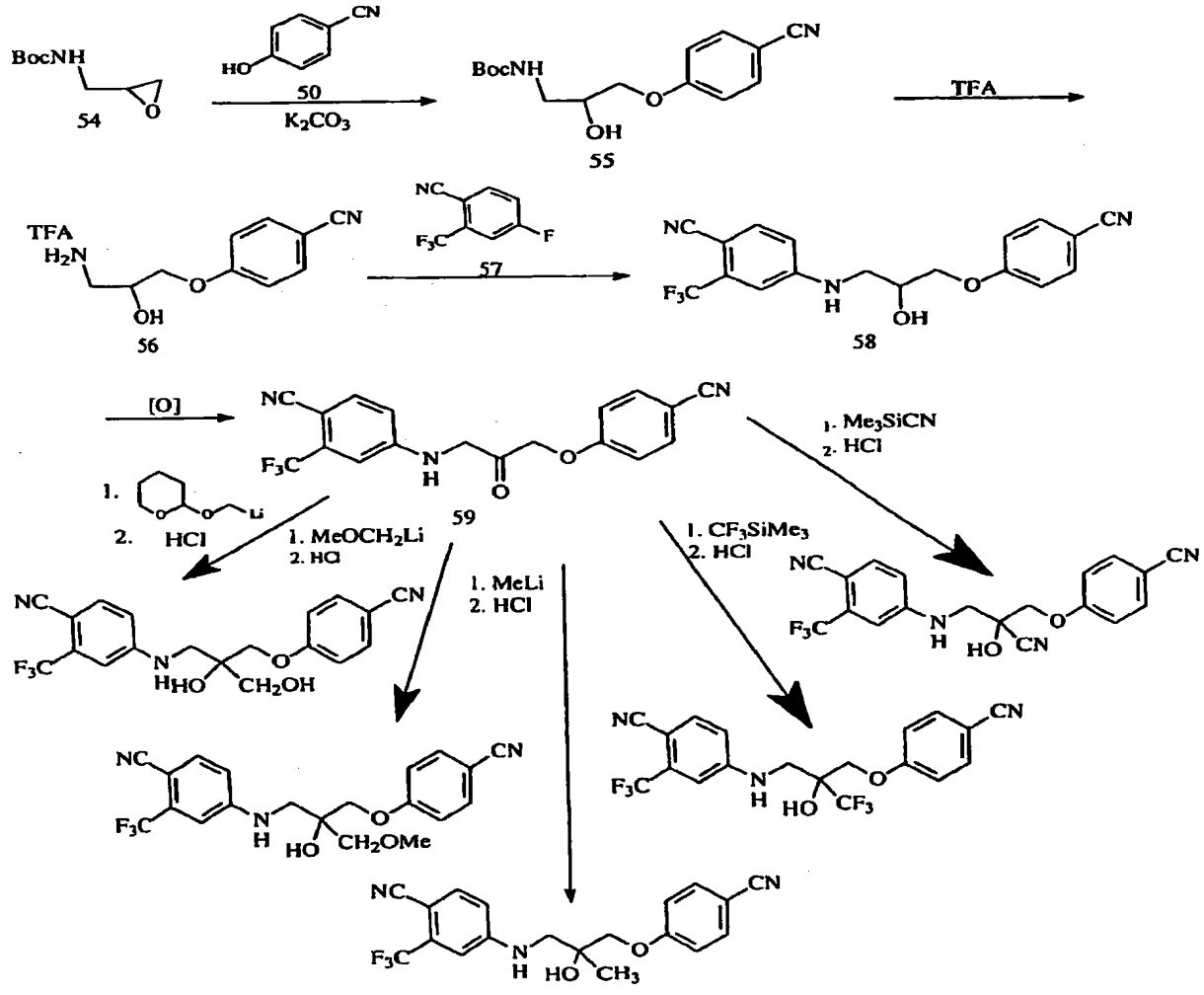

BocNH
54
50
K2CO3
55
TFA
H2N
56
57
58
[O]
59
1.
2. HCl
1. MeOCH2Li
2. HCl
1. MeLi
2. HCl
1. CF3SiMe3
2. HCl
1. Me3SiCN
2. HCl
CH2OH
CH2OMe
CF3
CH3
HO
CN
F3C
NC
N
H
O

图1D

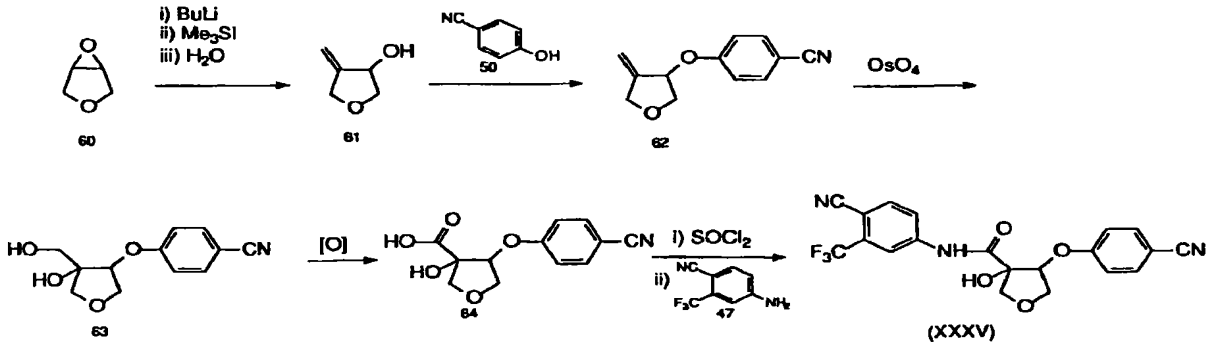


图1E

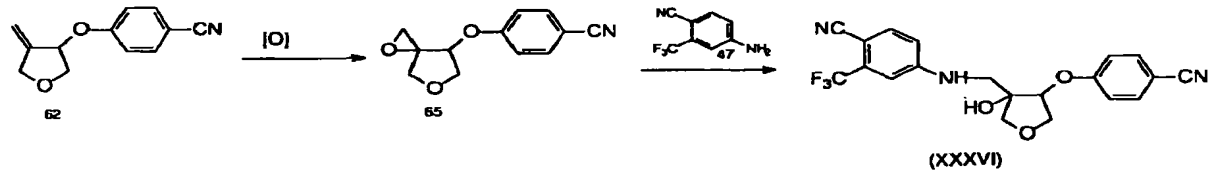


图1F

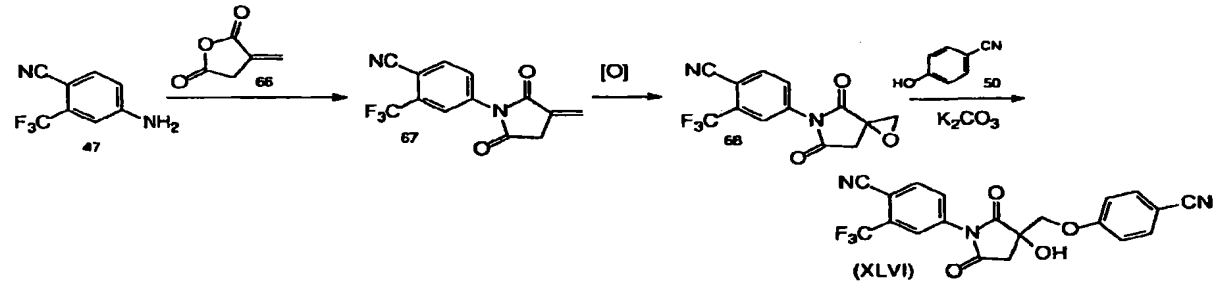


图1G

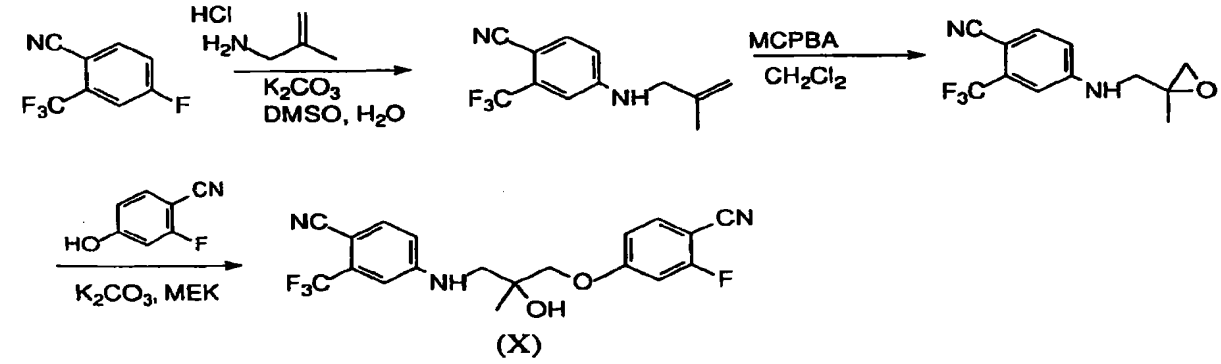
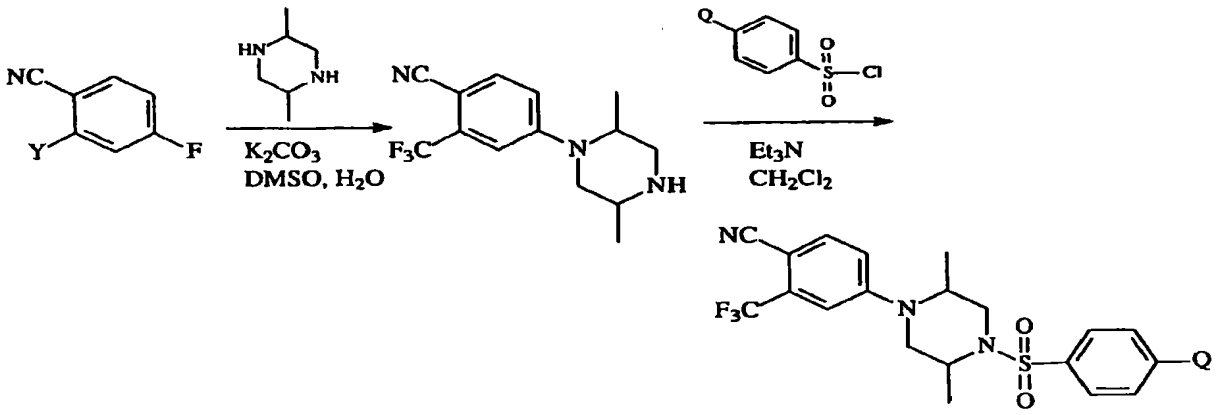
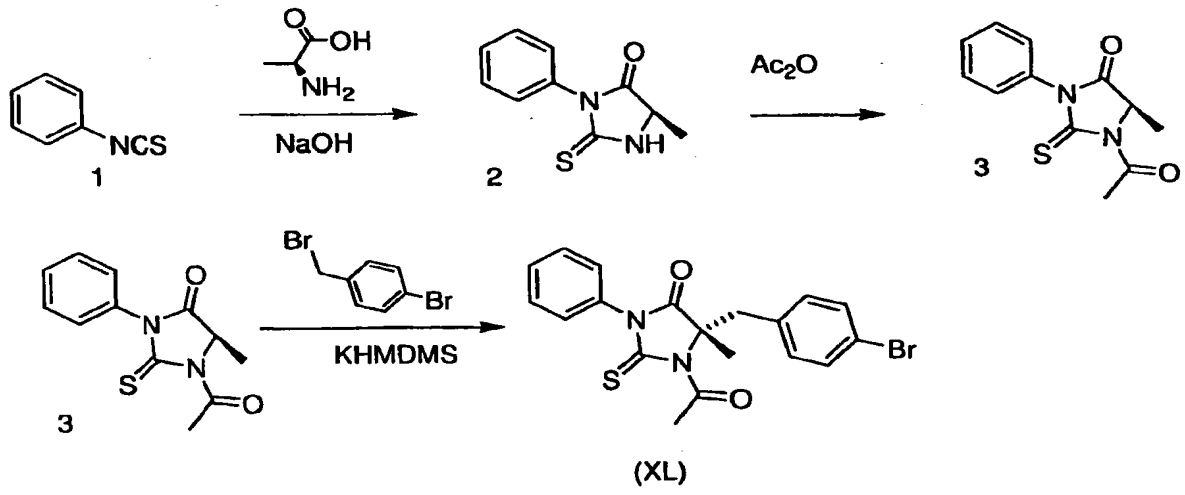


图1H



Q=CN, Y=CF_3 (化合物XXIV)
Q=CN, Y=Cl (化合物XXV)
Q=Cl, Y=CN (化合物XXVI)
Q=CF_3, Y=Cl (化合物XXVII)
Q=CF_3, Y=CF_3 (化合物XXVIII)

图1I



(XL)

图1J

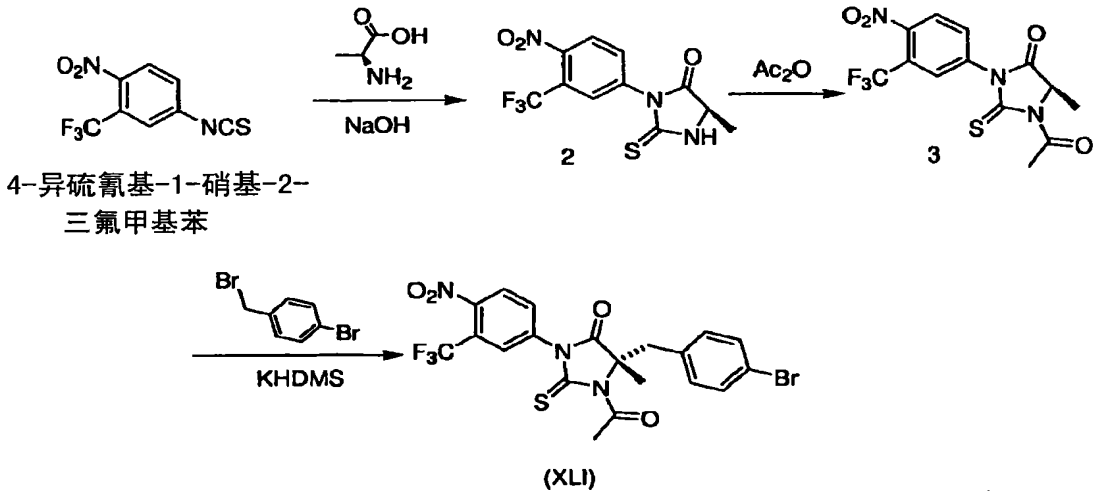
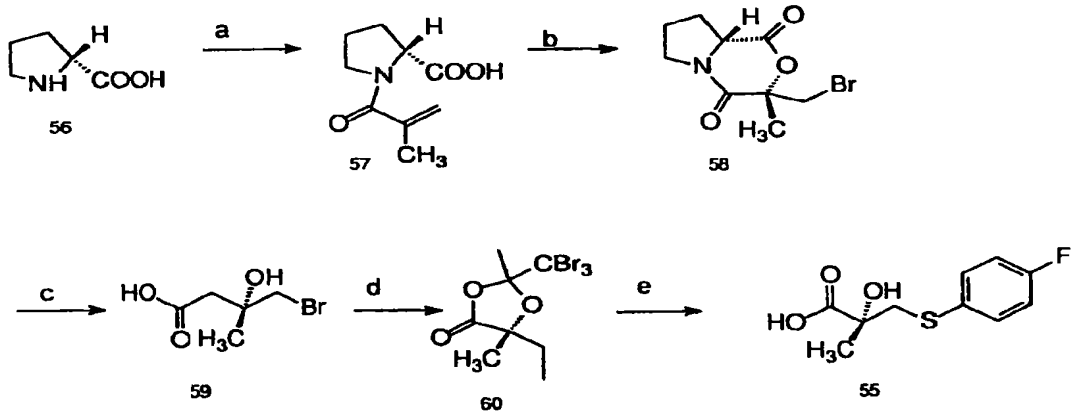
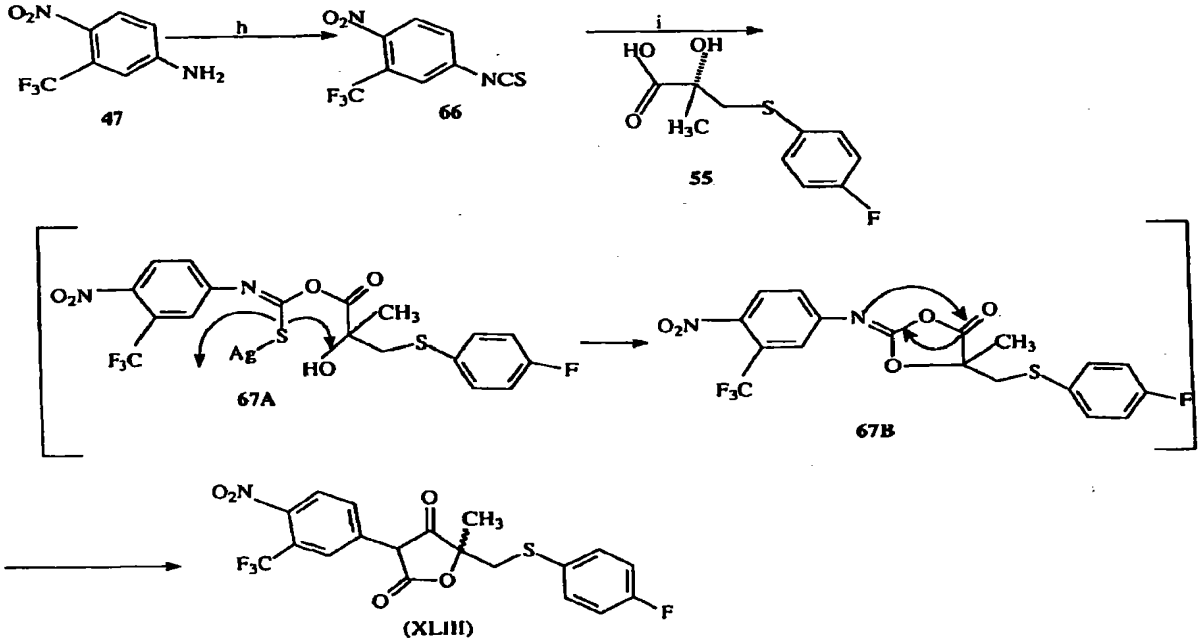


图1K



试剂： a -异丁烯酰氯、NaOH、丙酮； b-NBS、DMF； c-24%HBr；
d-三溴乙醛、浓硫酸； e- (1) NaOH、4-氟苯硫酚、2-丙醇， (2)浓HCl。



试剂：h-硫光气、氯仿、NaCO3， i-三氟乙酸银、三乙胺、乙腈。

图2

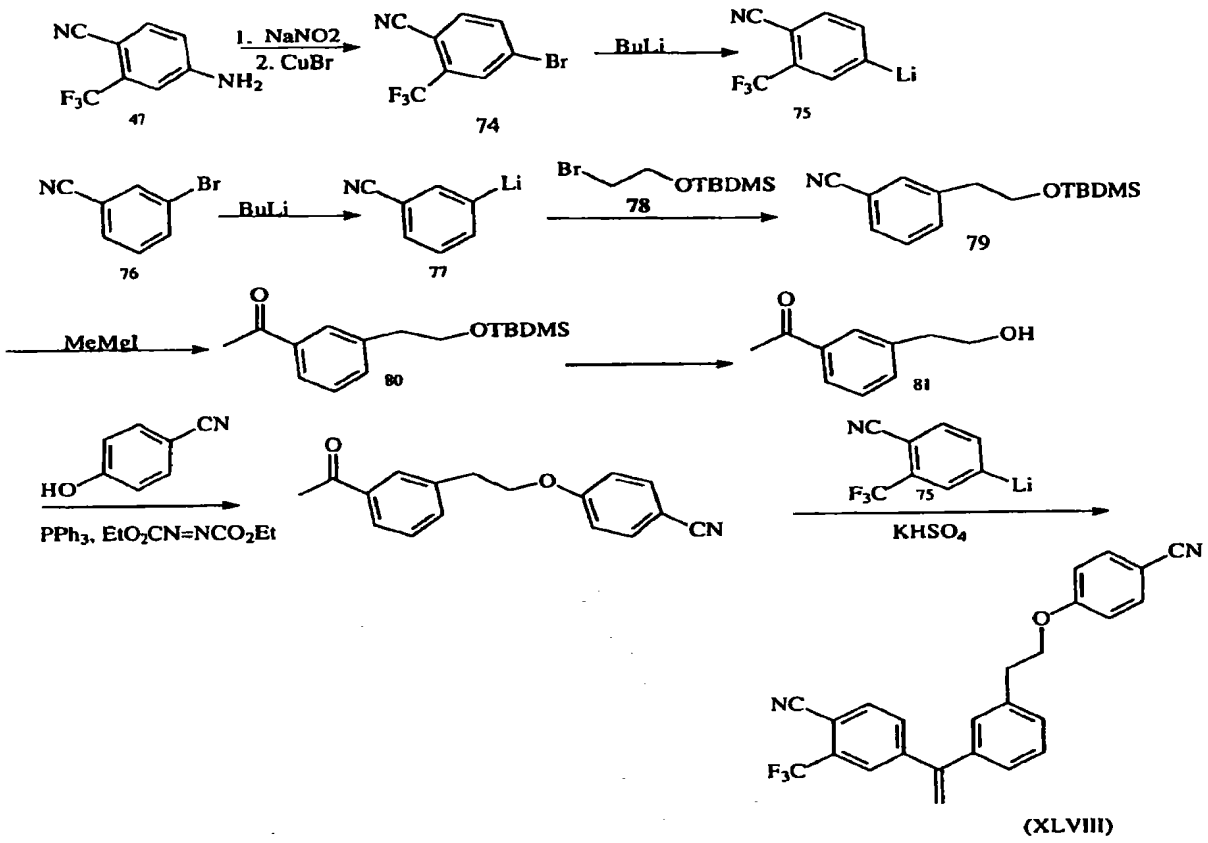

NC
1. NaNO2
2. CuBr
NH2
F3C
47
Br
74
BuLi
Li
75
76
77
78
OTBDMS
79
MeMgI
80
OH
81
HO
PPh3, EtO2CN=NCO2Et
KHSO4
(XLVIII)

图3

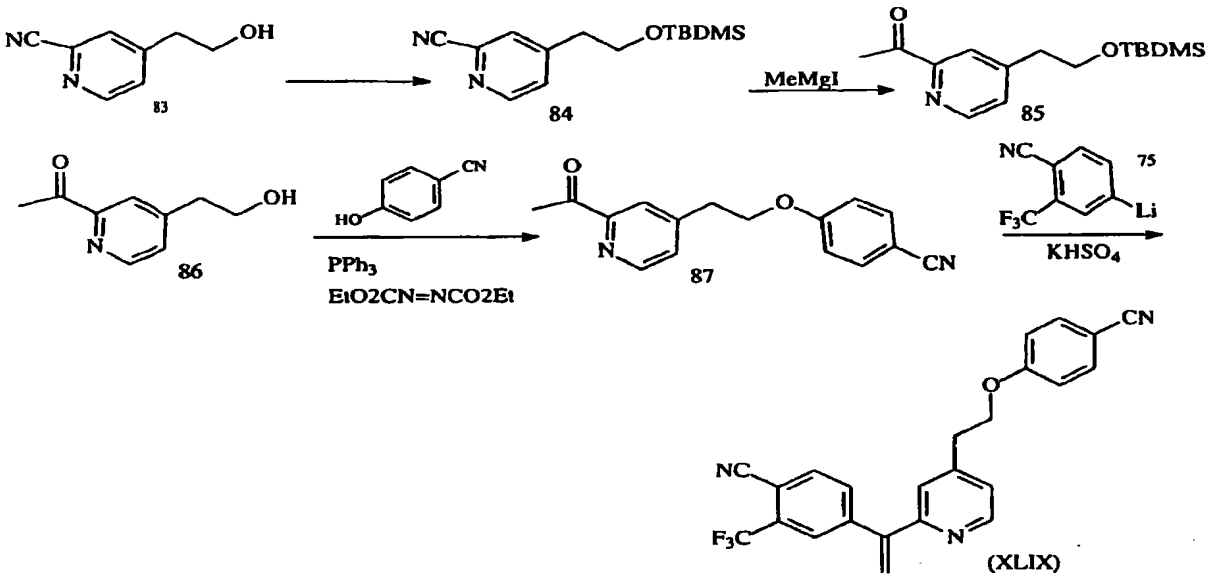

NC
OH
N
83
NC
OTBDMS
N
84
MeMgI
O
OTBDMS
N
85
O
OH
N
86
HO
CN
PPh3
EtO2CN=NCO2Et
O
N
O
CN
87
NC
75
F3C
Li
KHSO4
CN
O
NC
F3C
N
(XLIX)

图4

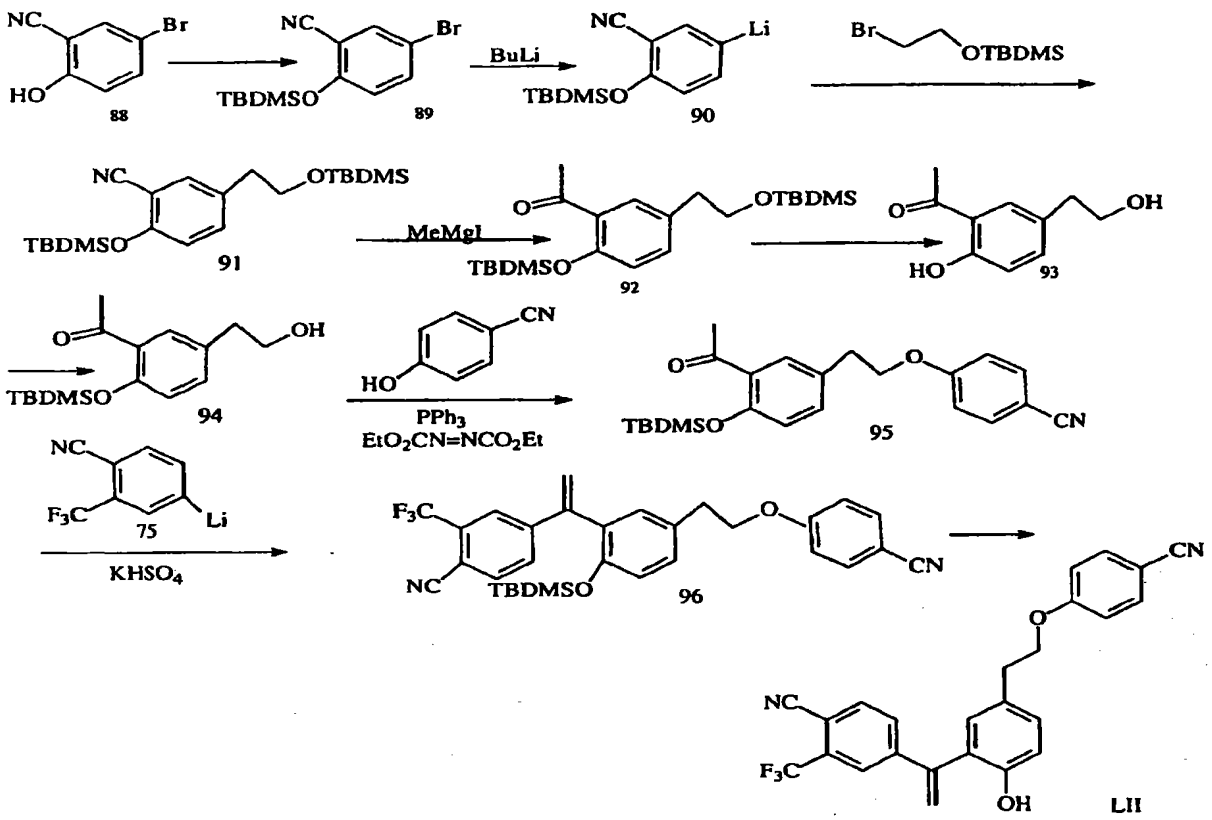

NC
Br
HO
88
TBDMSO
89
BuLi
Li
90
OTBDMS
91
MeMgI
92
OH
93
94
CN
PPh3
EtO2CN=NCO2Et
95
F3C
75
KHSO4
96
LII

图5

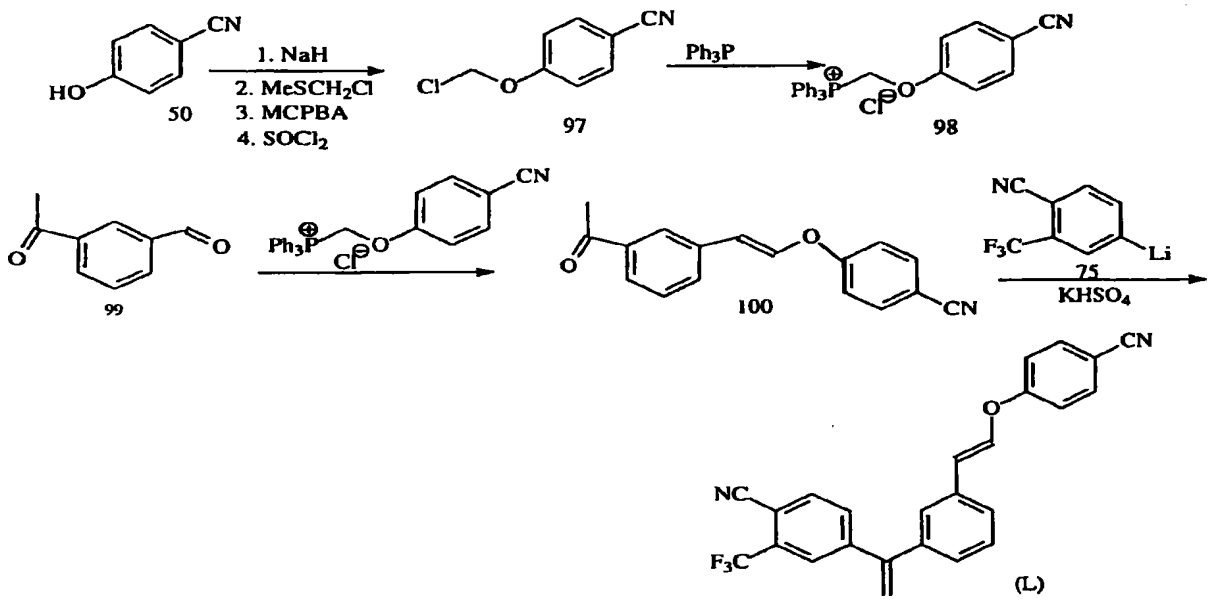

CN
HO
50
1. NaH
2. MeSCH2Cl
3. MCPBA
4. SOCl2
Cl
O
97
Ph3P
Ph3P
Cl
98
99
100
NC
F3C
Li
75
KHSO4
(L)

图6

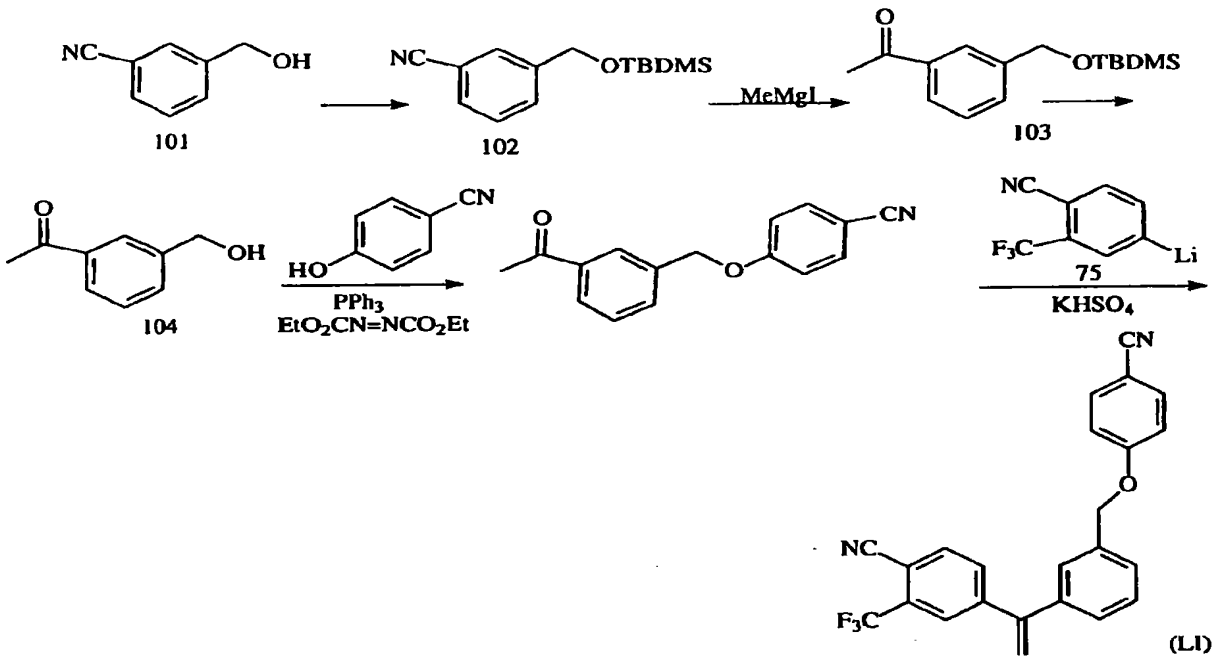

NC
OH
101
NC
OTBDMS
102
MeMgI
O
OTBDMS
103
O
OH
104
HO
CN
PPh3
EtO2CN=NCO2Et
O
CN
NC
F3C
Li
75
KHSO4
CN
O
NC
F3C
(LI)

图7

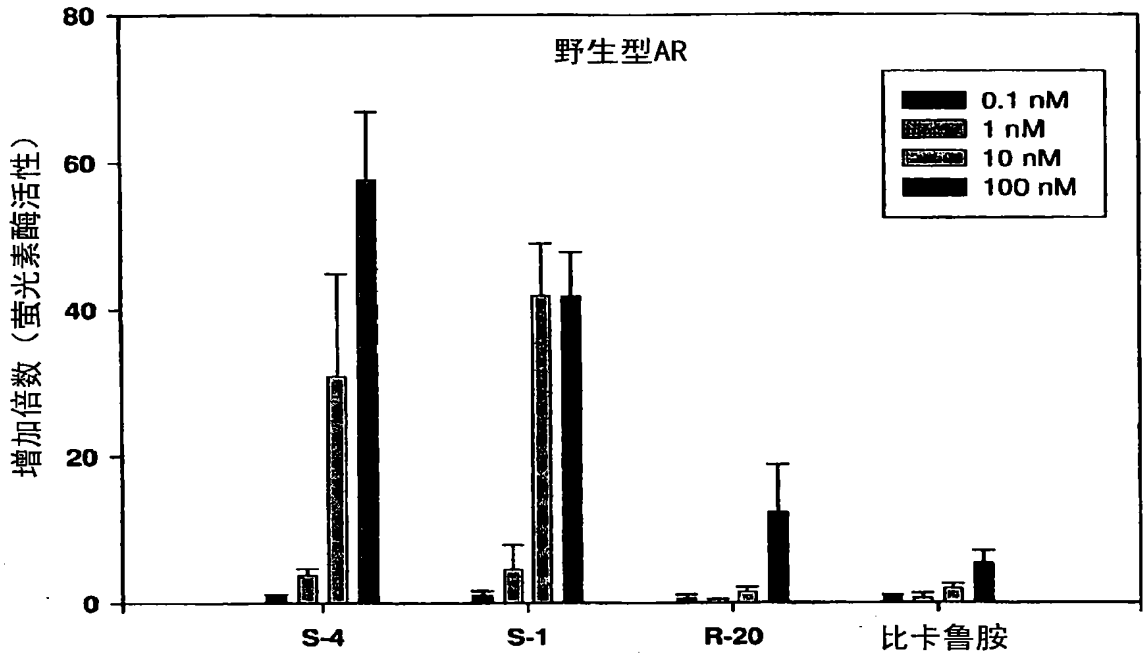

野生型AR
0.1 nM
1 nM
10 nM
100 nM
增加倍数（萤光素酶活性）
80
60
40
20
0
S-4
S-1
R-20
比卡鲁胺

图8

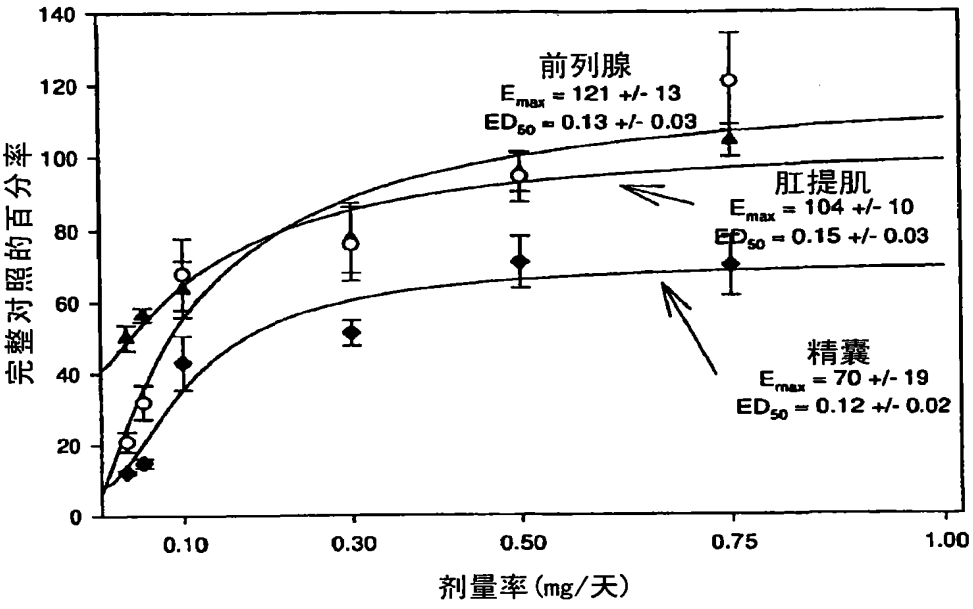

140
120
100
80
60
40
20
0
完整对照的百分率
前列腺
E_{max} = 121 +/- 13
ED_{50} = 0.13 +/- 0.03
肛提肌
E_{max} = 104 +/- 10
ED_{50} = 0.15 +/- 0.03
精囊
E_{max} = 70 +/- 19
ED_{50} = 0.12 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9A

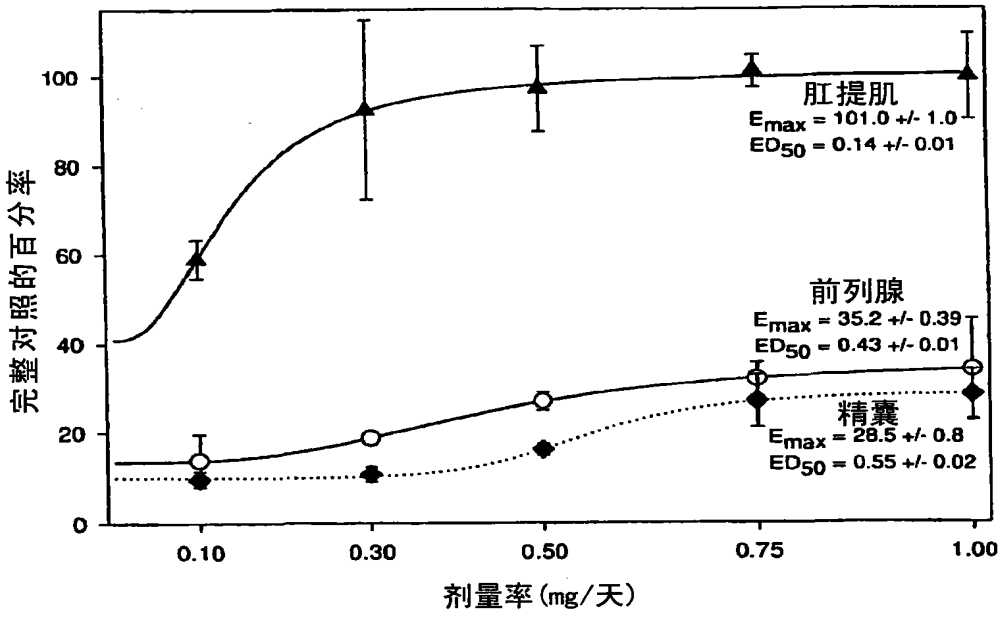

100
80
60
40
20
0
完整对照的百分率
肛提肌
E_{max} = 101.0 +/- 1.0
ED_{50} = 0.14 +/- 0.01
前列腺
E_{max} = 35.2 +/- 0.39
ED_{50} = 0.43 +/- 0.01
精囊
E_{max} = 28.5 +/- 0.8
ED_{50} = 0.55 +/- 0.02
0.10
0.30
0.50
0.75
1.00
剂量率(mg/天)

图9B

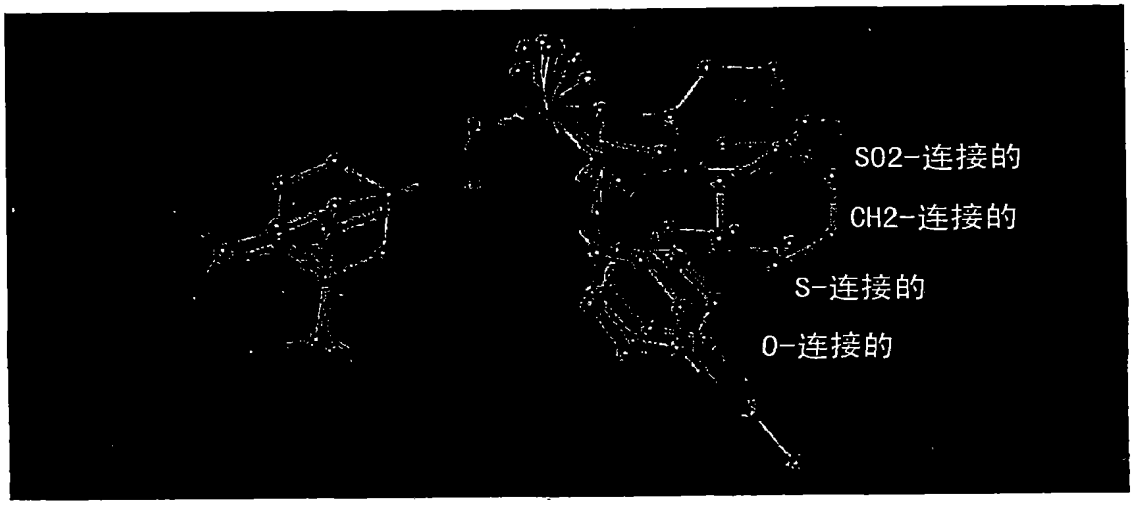


图10

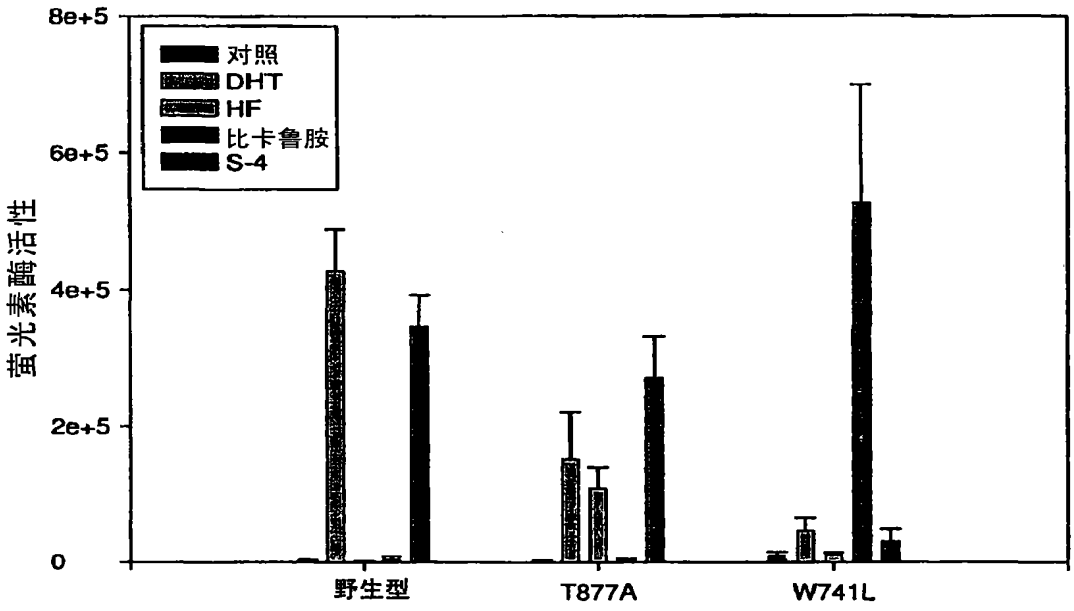


图11

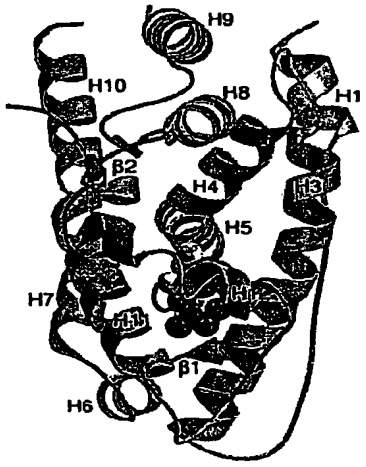

H9
H10
H8
H1
β2
H4
H3
H5
H7
H11
β1
H6

图12A

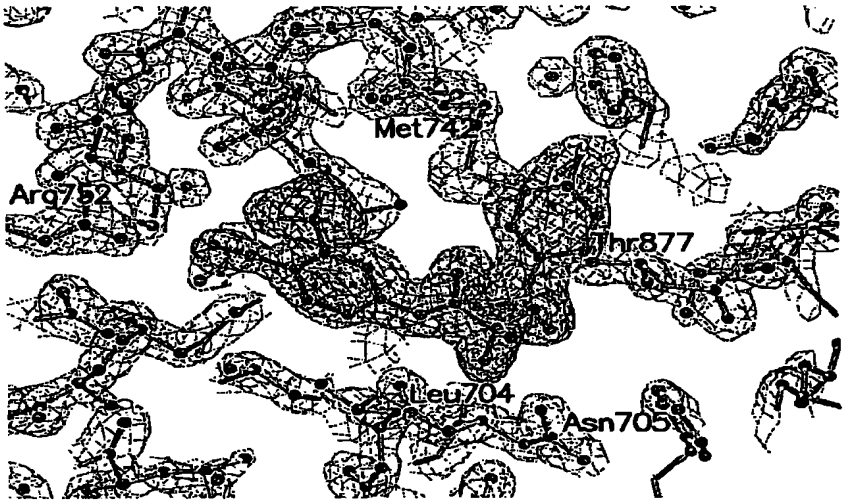
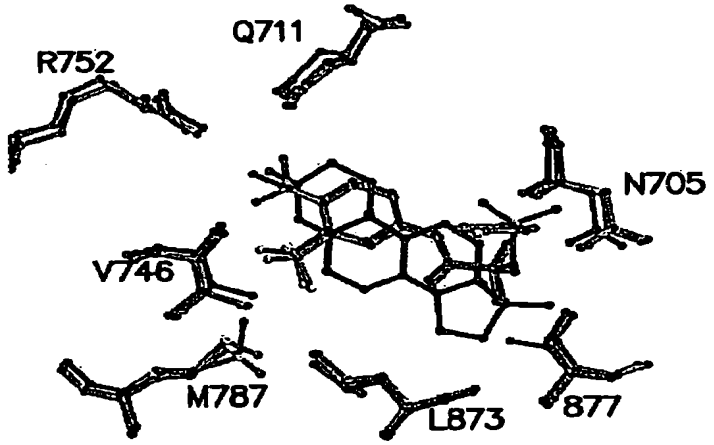

Met742
Arg752
Thr877
Leu704
Asn705

图12B



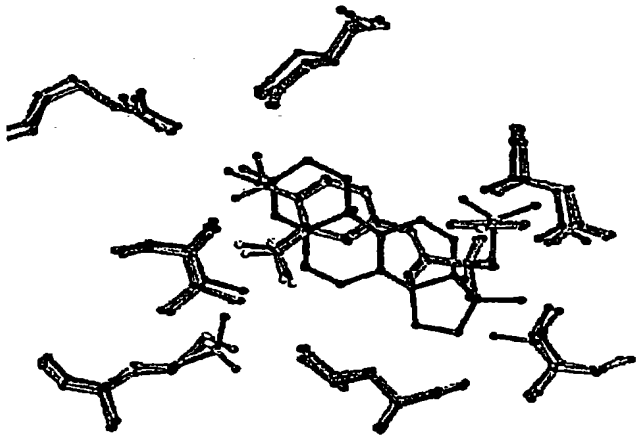


图13A

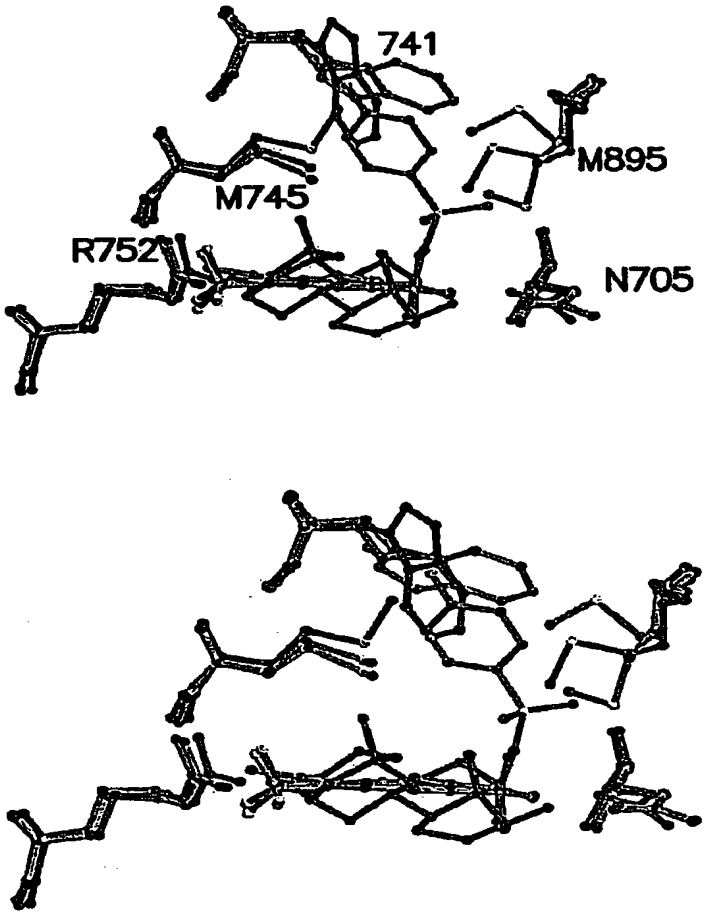


图13B

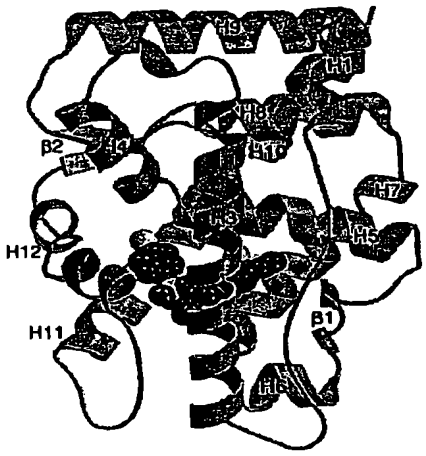

H9
H1
H8
β2
H3
H7
H6
H5
H12
H11
β1
H10

图14A

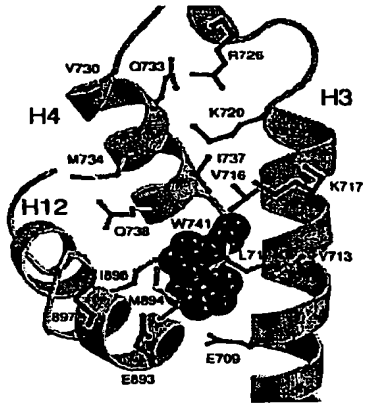

V730
Q733
R726
H4
K720
H3
M734
I737
V716
K717
H12
Q738
W741
L71
V713
I696
M694
S697
E709
E693

图14B

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
19/043,275	**08/13/2025 06:39:43 PM Z ET**	**50535-710.304**

Title of Invention

METHODS FOR TREATING TESTICULAR AND OVARIAN ADRENAL REST TUMORS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	5486	FILED BY	Jennifer Vail
PATENT CENTER #	71844803	FILING DATE	01/31/2025
CUSTOMER #	21971	FIRST NAMED INVENTOR	Alexis HOWERTON
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Kaia Parenti

Documents

TOTAL DOCUMENTS: 100

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
FOR_JP2000302693A_EFS.pdf	14	Foreign Reference	703 KB
FOR_EP2094709B1_EFS.pdf	38	Foreign Reference	1917 KB
FOR_WO0059908A2_EFS.pdf	118	Foreign Reference	3758 KB
FOR_WO02072202A1_EFS.pdf	56	Foreign Reference	1731 KB
FOR_WO0123388A2_EFS.pdf	102	Foreign Reference	4008 KB
FOR_EP3784233B1_EFS.pdf	83	Foreign Reference	6319 KB

FOR_WO9729109A1_EFS.pdf	44	Foreign Reference	1877 KB
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FOR_CN101516835A_EFS.pdf	215	Foreign Reference	10155 KB
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FOR_WO2005020910A2.pdf	155	Foreign Reference	5014 KB
FOR_WO2022036123A1_EFS.pdf	51	Foreign Reference	2482 KB
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FOR_WO2021016208A1_EFS.pdf	70	Foreign Reference	3692 KB
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NPL_ABCAM-CP154526-hydrochloride.pdf	2	Non Patent Literature	98 KB
NPL_AYCAN_Prevalence_long_667_672_2013.pdf	6	Non Patent Literature	619 KB
NPL_AVILA_Testicular_adrenal_1235_1238_1999.pdf	4	Non Patent Literature	911 KB

NPL_AUCHUS_Phase_trial_504_514_2024.pdf	15	Non Patent Literature	1161 KB
NPL_AUCHUS_Management_Considerations_190_197_2015.pdf	8	Non Patent Literature	1600 KB
NPL_CHEN-Recent-Advances-1261-1282.pdf	22	Non Patent Literature	312 KB
NPL_AUCHUS_Supplemental_Phase_504_514_2024.pdf	31	Non Patent Literature	3219 KB
NPL_CLAAHSEN_VAN_DER_GRINTEN_Prevalence_testicular_339_344_2007.pdf	6	Non Patent Literature	851 KB
NPL_CLAAHSEN_VAN_DER_GRINTEN_Repeated_successful_e5_e8_2007.pdf	4	Non Patent Literature	1216 KB
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NPL_DO-A-GENERAL-METHOD-COPPER-CATALYZED-15185-15192-2008.pdf	48	Non Patent Literature	1800 KB
NPL_ClinicalTrials_NCT04457336_1_17_2020.pdf	17	Non Patent Literature	3964 KB
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NPL_DO-COPPER-CATALYZED-ARYLATION-HETEROCYCLE-12404-12405.pdf	7	Non Patent Literature	263 KB
NPL_DAVE_Over_of_pharmaceutical_2008.pdf	52	Non Patent Literature	5745 KB
NPL_EP19793181_9_BriefCommunication_05Aug2025.p	24	Non Patent Literature	927 KB

df

NPL_EP19793181_9_ReplyfromOpponent_18July2025.pdf	8	Non Patent Literature	439 KB
NPL_ENGELS_Testicular_adrenal_973_987_2019.pdf	15	Non Patent Literature	3512 KB
NPL_EP19793181_9_Replyofthepatentproprietor_18Jun2025.pdf	26	Non Patent Literature	1786 KB
NPL_ESCOBAR-MORREALE-Polycystic-ovary-270-284.pdf	15	Non Patent Literature	828 KB
NPL_EP19793181_9_LetterofOpponent_2025MAR06.pdf	37	Non Patent Literature	3206 KB
NPL_Fuqua_DurationofSuppression_712549.pdf	8	Non Patent Literature	431 KB
NPL_CHEN-DESIGN-4787-4798.pdf	12	Non Patent Literature	16642 KB
NPL_GEHLERT_Novel_brain_2718_2726_2007.pdf	9	Non Patent Literature	793 KB
NPL_GILLIGAN-DISCOVERY-181-189.pdf	9	Non Patent Literature	135 KB
NPL_JOSEPH_Stress_HPA_1_15_2017.pdf	15	Non Patent Literature	1313 KB
NPL_Hodgetts_DiscoveryofN-1_4187-4206.pdf	20	Non Patent Literature	1652 KB
NPL_FLECK_Binding_Kinetics_518_531_2012.pdf	14	Non Patent Literature	4234 KB
NPL_Bornstein_DiagnosisandTreatment_364-389.pdf	26	Non Patent Literature	18340 KB
NPL_KHADILKAR-Can-polycystic-297-302.pdf	6	Non Patent Literature	713 KB
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NPL_MAJO-FACILE-PALLADIUM-620.pdf	5	Non Patent Literature	131 KB
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NPL_FAHMY_Structure_Function_270_281_2017.pdf	12	Non Patent Literature	6904 KB
NPL_MAZZILLI_TheHighPrevalenceof_335.pdf	6	Non Patent Literature	413 KB
NPL_MORABBI-Pexacerfont-Antagonist-1-9.pdf	9	Non Patent Literature	202 KB
NPL_MILLION-Novel-Water-32-42.pdf	11	Non Patent Literature	1226 KB
NPL_HE-4-1-3-DIMETHOXYPROP-449-456.pdf	8	Non Patent Literature	8654 KB
NPL_MALVERN-BASIC-GUIDE-PARTICLE-CHARACTERIZATION-2012.pdf	26	Non Patent Literature	4968 KB
NPL_NELLA_APhase2Study_4690-4698.pdf	9	Non Patent Literature	5667 KB
NPL_NEUROCRIN_V_SPRUCE_GroundsofInvalidity_31JAN2025.pdf	10	Non Patent Literature	110 KB
NPL_NEUROCRIN_V_SPRUCE_ParticularsofClaim_31JAN2025.pdf	2	Non Patent Literature	41 KB
NPL_NEUROCRIN_V_SPRUCE_Defence_13MAR2025.pdf	3	Non Patent Literature	48 KB
NPL_NEUROCRIN_V_SPRUCE_PatentOwnersResponse_08JUL2025.pdf	6	Non Patent Literature	142 KB
NPL_NEUROCRIN_V_SPRUCE_Memorandum_09JUN2025.pdf	10	Non Patent Literature	150 KB
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NPL_OREILLY_11_oxygenated_840_848_2017.pdf	9	Non Patent Literature	936 KB

NPL_NEUROCRINE_V_SPRUCE_PetitionersReplytoOwnersResp_20June2024_USPN10849908.pdf	38	Non Patent Literature	3093 KB
NPL_PCTUS2007078605-ISRWO-01-31-2008.pdf	18	Non Patent Literature	754 KB
NPL_NEUROCRINE_V_SPRUCE_PetitionersReplytoOwnersResp_20June2024_USPN11007201.pdf	36	Non Patent Literature	2649 KB
NPL_PCTUS2018046707_ISRWO.pdf	8	Non Patent Literature	393 KB
NPL_PCTUS2009058722-ISRWO-01-25-2010.pdf	13	Non Patent Literature	590 KB
NPL_PCTUS2018046760_ISRWO_24OCT2018.pdf	12	Non Patent Literature	1153 KB
NPL_PCTUS2021045780_ISRWO_17Dec2021.pdf	9	Non Patent Literature	400 KB
NPL_PCTUS2020042820-ISRWO-2020-11-25.pdf	10	Non Patent Literature	1369 KB
NPL_REISCH_High_prevalence_1665_1670_2009.pdf	6	Non Patent Literature	730 KB
NPL_PCTUS2022050436_ISRWO_20FEB2023.pdf	15	Non Patent Literature	1624 KB
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NPL_SARAFOGLOU-SUN-LB064-Supplement.pdf	3	Non Patent Literature	215 KB
NPL_Spruce_Biosciences_announces_1_4_2024.pdf	4	Non Patent Literature	787 KB
NPL_SARAFOGLOU_Tildacerfont_Adults_e4666_e4679_2021.pdf	22	Non Patent Literature	869 KB
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2013 (31.10.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/160317 A2

(51) **International Patent Classification**:
A61K 31/4412 (2006.01)

(21) **International Application Number**:
PCT/EP2013/058413

(22) **International Filing Date**:
23 April 2013 (23.04.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1207102.3 23 April 2012 (23.04.2012) GB
12165231.7 23 April 2012 (23.04.2012) EP

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2013/160317 A2

(54) **Title**: CRHR1 ANTAGONISTS FOR USE IN THE TREATMENT OF PATIENTS HAVING CRH OVERACTIVITY

(57) **Abstract**: The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in a novel group of patients, i.e. patients having corticotropin releasing hormone (CRH) overactivity.

CRHR1 antagonists for use in the treatment of patients having CRH overactivity

Field of the Invention

The present invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

Background of the Invention

While current antidepressant drugs are effective treatments of depression and anxiety symptoms in a number of psychiatric disorders, a large fraction of patients only show partial remission of symptoms or do not respond at all (Trivedi *et al.*, Am J Psychiatry, 2006). This may be due to the fact that these drugs do not target the inherent pathophysiologic disturbances leading to clinical condition in these patients. A number of novel antidepressant strategies, derived from both animal studies and human studies have been tested, but so far with little success. One of these approaches is the use of corticotropin releasing hormone receptor type 1 (CRHR1) antagonists. A wealth of data ranging from molecular studies in experimental animals to open label studies in human patients indicate that CRHR1 antagonists are a promising novel approach in the treatment of depression and anxiety (Ising *et al.*, Exp Clin Psychopharmacol, 2007; Holsboer *et al.*, CNS Spectr, 2001; Paez-Pereda *et al.*, Expert Opin Invest Drugs, 2011). However, so far all randomized clinical trials have failed to demonstrate the superiority of this drug to placebo (Coric *et al.*, Depress Anxiety, 2010; Binneman *et al.*, Am J Psychiatry, 2008).

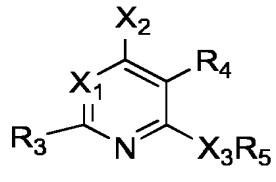
Hence, there is still a need for antidepressant drugs effective in the treatment of depression and/or anxiety symptoms in a number of psychiatric disorders.

It has now been found that despite the so far unsuccessful clinical trials, a specific group of patients, i.e. patients suffering from central corticotropin releasing hormone (CRH) overactivity, profits from the treatment with CRHR1 antagonists.

Summary of the Invention

One aspect of the invention relates to a corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

In an embodiment of the invention, the CRHR1 antagonist is a compound of formula (I)


(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is $-CR_6$ or N;

X_2 is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

X_3 is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or
X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}$

C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF_3, CF_3,

amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -NHCOCH$_3$ -NHCONHCH$_3$, -SO$_n$(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -NHCH$_3$, -N(CH_3)$_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO$_2$NH(C_1-C_4 alkyl), -SO$_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO$_2$NH$_2$, -NHSO$_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO$_2$(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF$_3$, CF$_3$, -CH$_2$OH, -CH$_2$OCH$_3$ or -CH$_2$OCH$_2$CH$_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

Further, CRHR1 antagonists of the invention encompass compounds of formula (I) as defined above, wherein X_1 is –CR$_6$. Optionally, in the CRHR1 antagonists of the invention X_1 is -CR$_6$, wherein R_6 is hydrogen.

In a further embodiment of the CRHR1 antagonists of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ of the compound of formula (I) as defined above is substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or SO_2 and one to four carbon atoms may optionally be replaced by nitrogen.

In a specific embodiment of the CRHR1 antagonists of the invention, X_2 of the compound of formula (I) as defined above is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

Optionally, in the compounds of formula (I) as defined above $-NHCHR_1R_2$ is -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$,, -$NHCH(CH_2CH_2OCH_3)_2$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, or $-NR_1R_2$ is -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or -$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$, or $-OCHR_1R_2$ is -$OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, -$OCH(CH_2CH_3)(CH_2OCH_3)$.

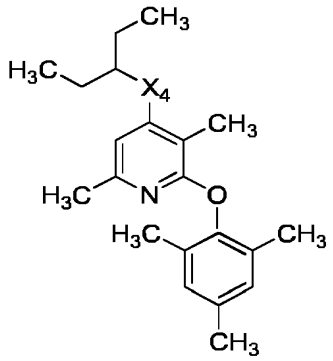
In another embodiment of the CRHR1 antagonists of the invention, R_3 and R_4 of the compound of formula (I) as defined above are methyl.

In a further embodiment of the CRHR1 antagonists of the invention, X_3 of the compound of formula (I) as defined above is O.

Another embodiment of the invention relates to the CRHR1 antagonists of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

A specific embodiment of the invention relates CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having

corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

In another specific embodiment, the CRHR1 antagonist of the invention is a class I or class II CRHR1 antagonist.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is DMP-696.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is CP 316,311.

In an exemplary embodiment of the present invention, the CRHR1 antagonist is SSR125543A.

Brief Description of the Drawings

Figure 1: Graph of the phenotypic distribution of ln(AAUC) at in-patient admission. The X-axis shows the ln of the AUC of the ACTH response and the Y-axis the frequency in total N/bin. The dashed vertical indicates the cut-off for being classified as a low vs. high responder. AAUC is the area under the curve of the ACTH response.

Figure 2: Increased REMS activity in CRH-COE^{CNS} mice is suppressed by DMP696 (50mg/kg/d) application via drinking water. Treatment day one, light grey; treatment day 2, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day one (+), two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

Figure 3: Increased activity of REMS in CRH-COE^{CNS} is suppressed by application of the CRH-R1 antagonist SSR125543 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black. Symbols indicate significant differences between baseline and treatment day two (#) or three (*). Light and dark bar on the x-axis indicate light and dark period, respectively.

Figure 4: REMS activity in Cor26 CRH mice is suppressed by application of the CRH-R1 antagonist CP-316311 (50mg/kg/d) via drinking water. Baseline day, white; treatment day two, dark grey; treatment day three, black.

Definitions

Where the term "comprise" or "comprising" is used in the present description and claims, it does not exclude other elements or steps. For the purpose of the present invention, the term "consisting of" is considered to be an optional embodiment of the

term "comprising of". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group which optionally consists only of these embodiments.

Where an indefinite or a definite article is used when referring to a singular noun such as "a" or "an" or "the", this includes a plural form of that noun unless specifically stated. Vice versa, when the plural form of a noun is used it refers also to the singular form. For example, when SNPs are mentioned, this is also to be understood as a single SNP.

Furthermore, the terms first, second, third or (a), (b), (c) and the like in the description and in the claims are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described or illustrated herein.

The term "corticotropin releasing hormone receptor 1" of "CRHR1" of "CRF_1" refers to the receptor which binds to corticotropin-releasing hormone.

The term "CRHR1 antagonist" refers to a compound capable of binding directly or indirectly to a CRH receptor 1 so as to modulate the receptor mediated activity. CRHR1 antagonists are well known in the literature and are e.g. described in WO 94/13676, EP 0 773 023, WO 2004/047866, WO 2004/094420, WO 98/03510, WO 97/029109, WO 2006/044958, WO 2001/005776 and WO 95/033750. Exemplary CRHR1 antagonists comprise NBI30775/R121919 (Neurocrine), CP316.311 (Pfizer), CP154,526 (Pfizer), Emicerfont (Glaxo), ONO-2333Ms (Ono Pharmaceutical), Pexacerfont (Bristol-Myers-Squibb), SSR125543 (Sanofi-Aventis), NBI-34101 (Neurocrine) and TAI041 (Taisho).

Most of the non-peptidic CRHR1 antagonists can be described by or adhere to a pharmacophore model that comprises or features a lipophilic top group, a

heterocyclic core containing an invariable hydrogen bond acceptor, which is almost always a heterocyclic nitrogen, and a lipophilic, usually aromatic, bottom group.

Class I CRHR1 antagonists as used herein may be characterized in that the heterocyclic hydrogen bond acceptor and the bottom group are connected by a two-atom linker as exemplified by CRHR1 antagonists R-121919, NBI-30545, CP-154526, DMP696, pexacerfont (BMS-562086), emicerfont (GW876008), or verucerfont (GSK561679). Class II CRF1R antagonists as used herein may be characterized by a two-atom linker between hydrogen bond acceptor and the bottom group as present in CRHR1 antagonist SSR125543A.

"Downstream target" or "molecule which is downstream of the CRHR1 receptor" as used herein may denote a molecule such as an endogenous molecule (e.g. peptide, protein, lipid, nucleic acid or oligonucleotide) that is regulated by CRHR1 directly or indirectly. The direct or indirect regulation may comprise direct or indirect modulation of the activity and/or expression level and/or localization, degradation, stability of the downstream target.

The term "normal CRH activity" refers to a range of CRH activity which can be found in human beings who are not affected by a condition which is associated with an increase of CRH activity (such as depression). A value indicative for normal CRH activity is usually considered to be indicative or predictive for a patient not responding to a treatment with a CRHR1 antagonist.

Further definitions of the terms will be given below in the context of which the terms are used.

Detailed Description of the Invention

While so far all randomized clinical trials have failed to demonstrate the superiority of CRHR1 antagonist to placebo in the treatment of depression and anxiety, it has now been found that a certain patient group, i.e. patients with corticotropin releasing

hormone (CRH) overactivity, is responsive to the treatment with corticotropin releasing hormone receptor type 1 (CRHR1) antagonists.

Hence, the present invention relates to CRHR1 antagonists for use in the treatment of depressive symptoms and/or anxiety symptoms in said novel patient group, i.e. patients having CRH overactivity.

The terms “CRH overactivity”, “CRH system overactivity”, “CRH hyperactivity”, “CRH hyperdrive” or "central CRH hyperdrive" are used herein interchangeable. An indication for CRH overactivity may be an increase in activity or concentration of CRH or of one or several molecules downstream of the CRHR1 receptor, that are activated or whose concentration is increased based on the activation of CRHR1 receptor upon CRH binding. A further indication for CRH overactivity may be a decrease in activity or concentration of one or several molecules downstream of the CRHR1 receptor, that are inactivated or whose concentration is decreased based on the activation of CRHR1 receptor upon CRH binding. A value indicative for CRH overactivity is usually considered to be indicative or predictive for a patient responding to a treatment with a CRHR1 antagonist. CRH activity vs. CRH overactivity may be defined relatively to the whole group, e.g. by using a median split of the area under the curve of the ACTH response in the dex/CRH test. Responses in the upper median may be categorized as being predictive of CRH overactivity, while responses in the lower median are indicative of normal CRH activity.

A “value indicative for CRH activity”, a "value indicative for CRH overactivity" and/or a "value indicative for normal CRH activity" can be obtained by determining the concentration or activity of CRH and/or of a downstream target of the CRHR1 receptor. The analysis is usually set up in a way that it can be excluded that the modulation of activity or concentration of a downstream target of the CRHR1 receptor is due to another disturbance than CRH activity. For instance, the concentrations or activities of adrenocorticotrophin (ACTH) and/or cortisol are useful biomarkers for determining a value indicative for CRH overactivity.

Typically, the CRH overactivity in each patient may be determined by measuring the ACTH and/or cortisol level response to a combined dexamethasone suppression/CRH stimulation test as described in Heuser *et al.* (J Psychiatr Res., 1994).

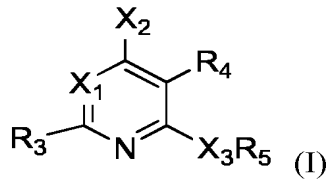
The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Patients suffering from depression normally show an increased release of cortisol and of adrenocorticotropic hormone (ACTH) in response to the combined treatment with dexamethasone and CRH as performed during the test, thus indicating a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Patients with a high HPA axis dysregulation show AUC values of cortisol of between 3000 and 18000 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 1000 and 6500 AUC units (pg/ml x 75 min). Patients having a low HPA axis dysregulation show AUC values of cortisol of between 300 and 2500 AUC units (ng/ml x 75 min) and/or AUC values of ACTH of between 250 and 1000 AUC units (pg/ml x 75 min) Various antidepressants lead to a reduction of these increased cortisol and ACTH levels in a combined dex/CRH test performed after the treatment with the antidepressants. Treatment response to antidepressants can thus be determined by performing a second dex/CRH test after treatment with the antidepressant and comparing the neuroendocrine response to the one shown in a combined dex/CRH test performed prior to treatment with the antidepressant.

In one embodiment of a combined dexamethasone suppression CRH stimulation test, subjects are pre-treated with dexamethasone and blood is drawn in certain intervals. Further, human CRH is administered after the first pretreatment with dexamethasone. Plasma ACTH and/or cortisol concentrations are then determined. The neuroendocrine response to the dex/CRH test may be analyzed using the total area under the curve (AUC) of the ACTH response. Details of an exemplary dex/CRH test are also described in Example 1 below.

Depressive symptoms comprise *inter alia* low mood, low self-esteem, loss of interest or pleasure, psychosis, poor concentration and memory, social isolation, psychomotor agitation/retardation, thoughts of death or suicide, significant weight change (loss/gain), fatigue, and feeling of worthlessness. The depressive disorders can last for weeks to lifelong disorder with periodic reoccurring depressive episodes. For the diagnosis of the depression mode (e.g. moderate or severe depression) the Hamilton Depression Rating Scale (HAM-D) (Hamilton, J Neurol Neurosurg Psychiatry, 1960) may be used. The depression mode may be also, in addition or alternatively, rated by alternative scales as the Beck Depression Inventory (BDI), the Montgomery-Åsberg Depression Scale (MADRS), the Geriatric Depression Scale (GDS), and/or the Zung Self-Rating Depression Scale (ZSRDS).

Anxiety symptoms comprise *inter alia* panic disorders, generalized anxiety disorder, phobias and posttraumatic stress disorder. Typical symptoms of anxiety are or include avoidance behavior which may lead to social isolation, physical ailments like tachycardia, dizziness and sweating, mental apprehension, stress and/or tensions. The strength of these symptoms ranges from nervousness and discomfort to panic and terror in humans or animals. Most anxiety disorders may last for weeks or even months, some of them even for years and worsen if not suitably treated. For measuring the severity of anxiety symptoms, the Hamilton Anxiety Rating Scale (HAM-A) and/or the State-Trait Anxiety Rating Scale (STAI) can be used.

A CRHR1 antagonist which may be used according to the invention in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is -CR_6 or N;

X_2 is -NR_1R_2, -$CR_1R_2R_9$, -$C(=CR_2R_{10})R_1$, -$NHCHR_1R_2$, -$OCHR_1R_2$, -$SCHR_1R_2$, -CHR_2OR_{10}, -CHR_2SR_{10}, -$C(S)R_2$ or -$C(O)R_2$;

X_3 is NH, O, S, -N(C_1-C_2 alkyl) or -$C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or
X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2,

-SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$ -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

In an embodiment of the invention, the CRHR1 antagonist of the present invention is a compound of formula (I) as defined above, wherein X_1 is –CR_6.

Alternatively, the CRHR1 antagonists of the invention encompass compound of formula (I) as defined above, wherein X_1 is N.

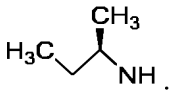
If X_1 is –CR_6, R_6 may be selected from the group consisting of hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$. In a specific embodiment of the CRHR1 antagonists of the invention R_6 is hydrogen.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (I) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -NR_1R_2.

In a specific embodiment, X_2 is –$NHCHR_1R_2$. In another specific embodiment, X_2 is –$OCHR_1R_2$. In a further specific embodiment, X_2 is –NR_1R_2.

If X_2 is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically X_2 is -$NHCH(CH_2CH_3)_2$. Alternatively, X_2 is -$NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is -$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is –

$NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $-NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or-$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is -$OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (I) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (I) is C_1 alkyl. In a further embodiment of the invention R_1 of formula (I) is C_2 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_3 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_4 alkyl. In a further embodiment, of the invention, R_1 of formula (I) is C_5 alkyl. In a further embodiment of the invention, R_1 of formula (I) is C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the

(C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, R_2 of formula (I) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (I) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and

-SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR_1R_2, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is –NHCR_1R_2, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

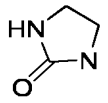
In another embodiment of the invention X_2 is -NR_1R_2 which forms a 5- to 8-membered ring. In a further embodiment of the invention X_2 is –C$R_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR_1R_2 or –C$R_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur

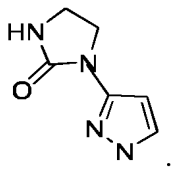
atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (I) as defined above, wherein X_3 is NH, O, NCH_3, or N, whereby, if X_3 is N, X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. Specifically, X_3 of formula (I) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with

R_5. More specifically, X_3 of formula (I) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5 wherein X_3 and R_4 form a group –N-CH_2CH_2-. Alternatively, X_3 is O or NH, more specifically X_3 is O.

The CRHR1 antagonist of the invention further encompasses a compound of formula (I) as defined above, wherein R_3 is methyl. In a further embodiment of the invention, R_4 of formula (I) as defined above is C_1-C_4 alkyl. Optionally R_4 of formula (I) as defined above is methyl. Alternatively, R_4 of formula (I) as defined above is ethyl. The present invention also encompasses CRHR1 antagonists wherein both R_3 and R_4 are methyl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention,

the CRHR1 antagonist encompasses a compound of formula (I) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3.

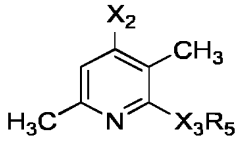
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

In a specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (II)



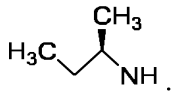
(II),

wherein X_2, X_3, R_1, R_2 und R_5-R_{12} are as defined above for formula (I).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (II) as defined above, wherein X_2 is selected from the group consisting of $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $-NHCHR_1R_2$. In another specific embodiment, X_2 is $-OCHR_1R_2$. In a further specific embodiment, X_2 is $-NR_1R_2$.

If X_2 is $-NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $-NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (II) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (II) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (II) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and/or the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (II) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (II) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR_1R_2, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-

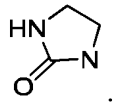
C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is $-NHCR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

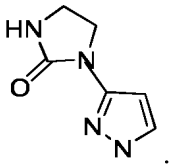
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

A further embodiment of the invention encompasses CRHR1 antagonists of formula (II) as defined above, wherein X_3 is NH, O, NCH_3, or N, whereby if X_3 is N, X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. Specifically, X_3 of formula (II) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5. More specifically, X_3 of formula (II) as defined above is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5, wherein X_3 and R_4 form a group $-N\text{-}CH_2CH_2-$. Alternatively, X_3 is O or NH, more specifically X_3 is O.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl,

F, CF_3. In a specific embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (II) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

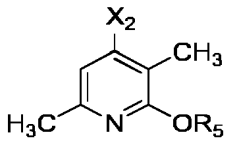
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl, or 2,4-dimethoxy-phenyl. More specifically R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (III)

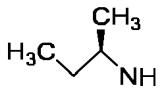

(III),

wherein X_2, R_1, R_2 und R_5-R_{10} are as defined for formulas (I) and (II) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (III) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, -$OCHR_1R_2$ or -NR_1R_2.

In a specific embodiment, X_2 is –$NHCHR_1R_2$. In another specific embodiment, X_2 is –$OCHR_1R_2$. In a further specific embodiment, X_2 is –NR_1R_2.

If X_2 is –$NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, -$NHCH(CH_2OCH_3)(CH_2CH_3)$, -$NHCH(CH_2CH_3)_2$, -$NHCH(CH_2CH_2OCH_3)_2$, -$NHCH(CH_3)(CH_2CH_3)$ or -$NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is -$NHCH(CH_2CH_3)_2$. Alternatively, X_2 is -$NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is –$NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is –$NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is –$NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is –NR_1R_2, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, -$N(CH_2CH_2CH_3)_2$, -$N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, -$N(CH_2CH_2OCH_3)_2$, or -$N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. More specifically, X_2 is –$N(CH_2OCH_3)_2$. Alternatively, X_2 is -$N(CH_2CH_2OCH_3)_2$.

If X_2 is -$OCHR_1R_2$, it is optionally selected from –$OCH(CH_2CH_3)_2$, –$OCH(CH_2CH_3)CH_3$, –$OCH(CH_2CH_3)(CH_2CH_2CH_3)$, or –$OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is –$OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention may encompass compounds of formula (III) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (III) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (III) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (III) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (III) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl.

In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –$NHCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7

independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is –NHCR_1R_2, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is -NR_1R_2 which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is –C$R_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR_1R_2 or –C$R_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

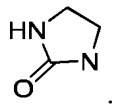
In a specific embodiment, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by –NR_1R_2 is a pyrazol-1-yl. Alternatively, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by –NR_1R_2 or –C$R_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring.

In one embodiment of the invention, the 5- to 8-membered ring formed by –NR_1R_2 or –C$R_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8

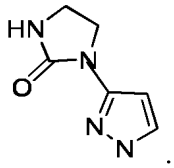
membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



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Optionally, X_2 is



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In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one

carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the ring carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another embodiment of the invention, the CRHR1 antagonist is a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-SO_2NH$(C_1-C_4 alkyl), $-SO_2N$(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and SO_2(C_1-C_6 alkyl). The C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl.

In an embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In a specific embodiment of the invention, the CRHR1 antagonist

encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with one substituent independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with two substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3. In another embodiment of the invention, the CRHR1 antagonist encompasses a compound of formula (III) as defined above, wherein R_5 is phenyl substituted with three substituents independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, and CF_3.

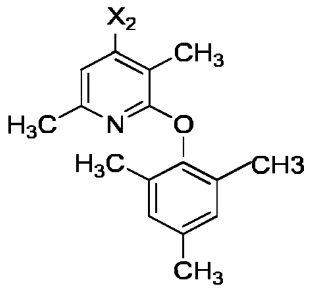
In a specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with two substituents, wherein the two substituents are CH_3 and OCH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, R_5 is phenyl substituted with three substituents, wherein the three substituents are CH_3.

In another specific embodiment of the CRHR1 antagonist of the invention, the three substituents of said phenyl are independently selected from CH_3 and Cl.

Specifically, R_5 is 2-chloro-4-methoxy-5-methyl-phenyl, 2,4,6-trimethyl-phenyl, 2,4,6-trichloro-phenyl, 4-methoxy-2-methyl-phenyl, 2,4-dichloro-phenyl, 4-chloro-2,6-dimethyl-phenyl, 2,4-dimethyl-phenyl or, 2,4-dimethoxy-phenyl. More specifically, R_5 is 2,4,6-trimethyl-phenyl or 4-chloro-2,6-dimethyl-phenyl. Even more specifically, R_5 is 4-chloro-2,6-dimethyl-phenyl.

Another specific embodiment of the invention relates to a CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein the CRHR1 antagonist is a compound of formula (IV)



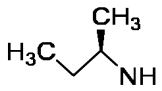
(IV),

wherein X_2, R_1, R_2, R_7, R_8, R_9 and R_{10} are as defined above for formulas (I) to (III).

A further embodiment of the invention relates to a CRHR1 antagonist of formula (IV) as defined above, wherein X_2 is selected from the group consisting of –$NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $–NHCHR_1R_2$. In another specific embodiment, X_2 is $–OCHR_1R_2$. In a further specific embodiment, X_2 is $–NR_1R_2$.

If X_2 is $–NHCHR_1R_2$, it is optionally selected from the group consisting of -$NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH)_3(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $-NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $–NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $–NR_1R_2$, it is optionally selected from the group consisting of -$N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), -

$N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $-N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $-OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $-OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (IV) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (IV) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (IV) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of $-CH_2OCH_3$, $-CH_2CH_2OCH_3$ and $-CH_2$-cyclopropyl.

In another embodiment of the invention, R_2 of formula (IV) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (IV) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively, each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is $-NHCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and/or the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is $-NHCR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

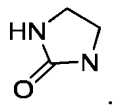
In another embodiment of the invention, X_2 is -NR_1R_2 which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by -NR_1R_2 or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

In a specific embodiment, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, -NR_1R_2 forms a 5-membered ring containing two double bonds, wherein one of the ring carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring

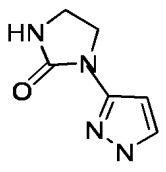
formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



.

Optionally, X_2 is



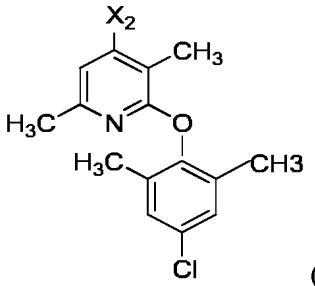
.

In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally,

one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5-membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$, containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom, is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$,containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-dialkylpyrazol-1-yl, such as 3,5-diethylpyrazol-1-yl.

In another specific embodiment of the invention, the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (V)



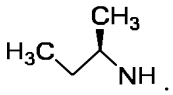
(V)

or a pharmaceutically acceptable salt thereof, wherein X_2, R_1, R_2, R_7, R_8, R_9 and R_{10} are as defined for formulas (I)-(IV) above.

A further embodiment of the invention relates to a CRHR1 antagonist of formula (V) as defined above, wherein X_2 is selected from the group consisting of $–NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

In a specific embodiment, X_2 is $–NHCHR_1R_2$. In another specific embodiment, X_2 is $–OCHR_1R_2$. In a further specific embodiment, X_2 is $–NR_1R_2$.

If X_2 is $–NHCHR_1R_2$, it is optionally selected from the group consisting of $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl. More specifically, X_2 is $-NHCH(CH_2CH_3)_2$. Alternatively, X_2 is $-NHCHR_1R_2$ wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl. Alternatively, X_2 is $–NHCH(CH_2CH_2OCH_3)_2$. Alternatively, X_2 is $-NHCH(CH_2OCH_3)_2$. Alternatively, X_2 is $–NHCH(CH_3)(CH_2CH_3)$. More specifically, X_2 is



Alternatively, if X_2 is $–NR_1R_2$, it is optionally selected from the group consisting of $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)(CH_2$-cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$. Alternatively, X_2 is $–N(CH_2CH_2OCH_3)_2$.

If X_2 is $-OCHR_1R_2$, it is optionally selected from $–OCH(CH_2CH_3)_2$, $–OCH(CH_2CH_3)CH_3$, $–OCH(CH_2CH_3)(CH_2CH_2CH_3)$ or $–OCH(CH_2CH_3)(CH_2OCH_3)$. More specifically, X_2 is $–OCH(CH_2CH_3)_2$.

Further CRHR1 antagonists for use according to the invention encompass compounds of formula (V) as defined above wherein R_1 is C_1-C_6 alkyl.

In another embodiment of the invention, R_1 of formula (V) is a C_1 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_2 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_3 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_4 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_5 alkyl. In a further embodiment of the invention, R_1 of formula (V) is a C_6 alkyl.

Any of the aforementioned R_1 groups may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl). Said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond.

Specifically, R_1 is C_1-C_6 alkyl substituted with substituent R_7 selected from the group consisting of F, CF_3, C_1-C_4 alkoxy and C_3-C_8 cycloalkyl. More specifically, R_1 is selected from the group consisting of –CH_2OCH_3, -$CH_2CH_2OCH_3$ and –CH_2-cyclopropyl.

In another embodiment of the invention, R_2 of formula (V) is C_1-C_{12} alkyl. In another embodiment of the invention, R_2 of formula (V) is C_1-C_{12} alkoxyalkyl. In a further embodiment, R_2 is aryl. In another embodiment, R_2 is -(C_1-C_4 alkylene)aryl. In a further embodiment of the invention, R_2 is a 3- to 8-membered cycloalkyl. In another embodiment of the invention, R_2 is a –(C_1-C_6 alkylene)cycloalkyl.

Optionally, if the R_2 group is aryl or –(C_1-C_4 alkylene)alkyl, said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl,

benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl. More specifically, R_2 is oxadiazolyl.

Optionally, if the R_2 group is a 3- to 8-membered cycloalkyl or a –(C_1-C_6 alkylene)cycloalkyl, one or two of the ring carbons of said cycloalkyl having at least 4 ring members and/or the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl.

Each of the aforementioned R_2 groups may be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Alternatively each of the aforementioned R_2 groups may be substituted with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl). Optionally, said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may contain one carbon-carbon double or triple bond.

In a specific embodiment of the invention, R_2 is aryl substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl. Optionally, R_2 is aryl substituted with one substituent selected from chloro, fluoro and C_1-C_4 alkyl. More specifically, R_2 is oxadiazolyl substituted with one substituent independently selected from chloro, fluoro, C_1-C_4 alkyl, CF_3 and cyclopropyl. Even more specifically, R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is –NHCHR_1R_2, wherein R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and/or the

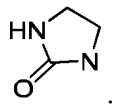
(C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond and R_2 is oxadiazolyl substituted with methyl. Optionally, X_2 is $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl.

In another embodiment of the invention, X_2 is $-NR_1R_2$ which forms a 5- to 8-membered ring. In a further embodiment of the invention, X_2 is $-CR_1R_2R_9$ which forms a saturated 5- to 8-membered ring. The ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ optionally contains one or two carbon-carbon double bonds. Alternatively or additionally, one or two of the ring carbons may be replaced by an oxygen, nitrogen or sulfur atom.

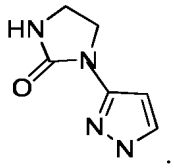
In a specific embodiment, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by an oxygen, nitrogen or sulfur atom. Optionally, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom. More specifically, the 5-membered ring formed by $-NR_1R_2$ is a pyrazol-1-yl. Alternatively, $-NR_1R_2$ forms a 5-membered ring containing two double bonds, wherein one of the rings carbons is replaced by a sulfur atom.

The above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ may be substituted with at least one substituent selected from C_1-C_4 alkyl or with a 4-8 membered ring. In one embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with one substituent selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with two substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with three substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring. In another embodiment of the invention, the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with four substituents independently selected from C_1-C_4 alkyl or a 4-8 membered ring.

Said 4-8 membered ring may be saturated or may contain one to three double bonds. Optionally, the 4-8 membered ring is saturated. Additionally, one carbon atom of said 4-8 membered ring may be replaced by CO. Alternatively, one carbon atom of said 4-8 membered ring may be replaced by SO_2. Alternatively or additionally, one to four carbon atom(s) of the 4-8 membered ring may be replaced by nitrogen. Optionally, two carbon atoms are replaced by nitrogen. More specifically, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by CO. Alternatively, two carbon atoms of the 4-8 membered ring are replaced by nitrogen and one carbon atom is replaced by SO_2. In a specific embodiment of the invention the above described 5- to 8-membered ring formed by $-NR_1R_2$ is substituted with



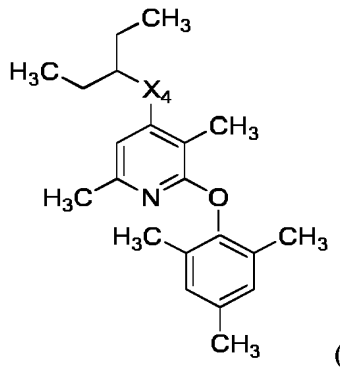
Optionally, X_2 is



In an alternative embodiment, the 4-8 membered ring contains one to three double bonds. Optionally, the 4-8 membered ring contains two double bonds. Additionally, one carbon atom of the 4-8 membered ring may be replaced by nitrogen and one carbon atom may be replaced by sulfur. Optionally, the above described ring is a 5 membered ring. In a specific embodiment of the invention, the above described 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with thiazol. Optionally, X_2 is a 5-membered ring formed by $-NR_1R_2$ containing two double bonds, wherein one of the rings carbons is replaced by a nitrogen atom and wherein said 5-membered ring is substituted with thiazol.

In a specific embodiment of the invention, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with at least one C_1-C_4 alkyl. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with two C_1-C_4 alkyl substituents. In another embodiment, the 5-membered ring formed by $-NR_1R_2$ containing two double bonds and wherein one carbon atom is replaced by a nitrogen atom is substituted with three C_1-C_4 alkyl substituents. Optionally, X_2 is 3,5-Dialkylpyrazol-1-yl, more specifically 3,5-Diethylpyrazol-1-yl.

In another specific embodiment of the invention the CRHR1 antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity is a compound of formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

In another embodiment of the invention, the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965, SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

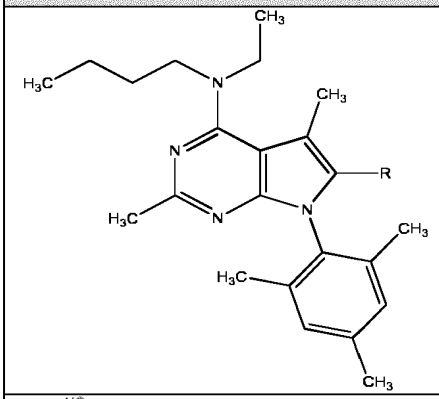
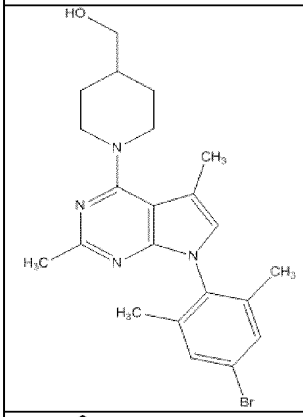
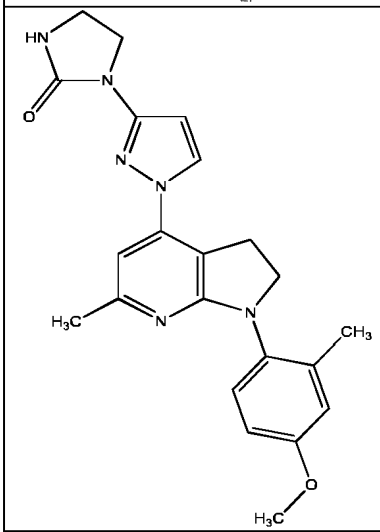
In a particular embodiment of the invention, the CRHR1 antagonist is DMP-696.

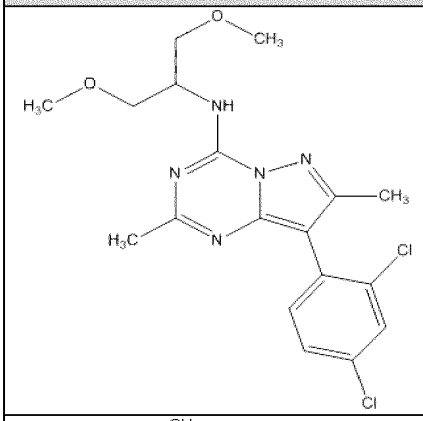
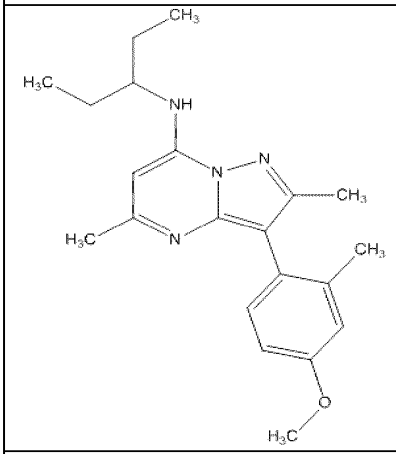
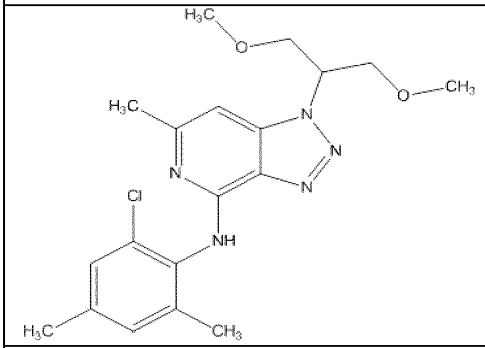
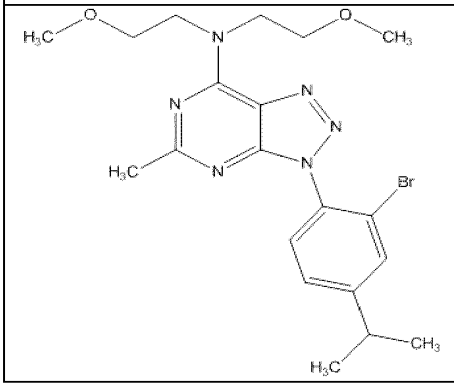
In a particular embodiment of the invention, the CRHR1 antagonist is CP-316,311.

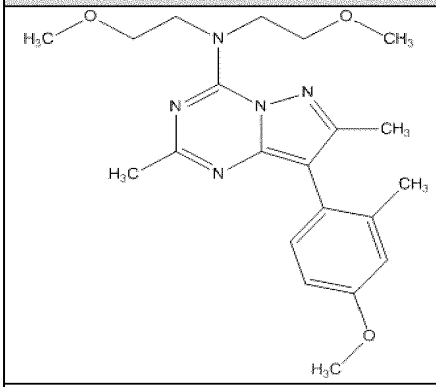
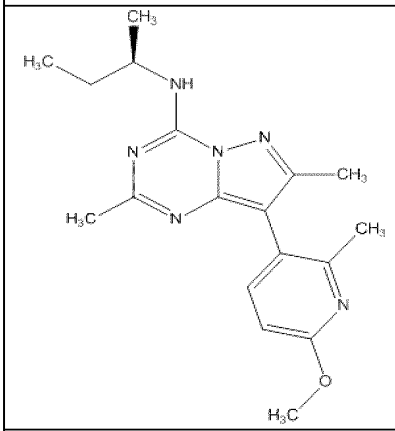
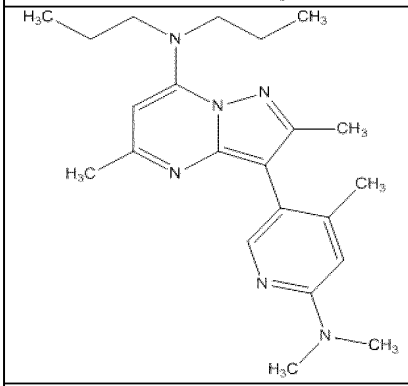
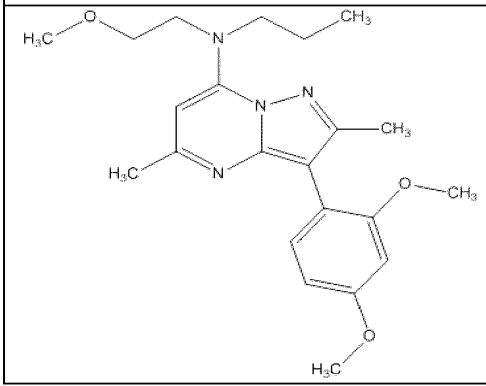
In a particular embodiment of the invention, the CRHR1 antagonist is SSR125543A

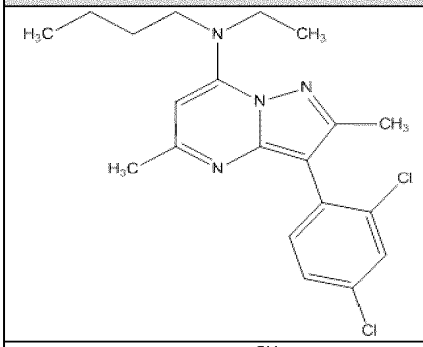
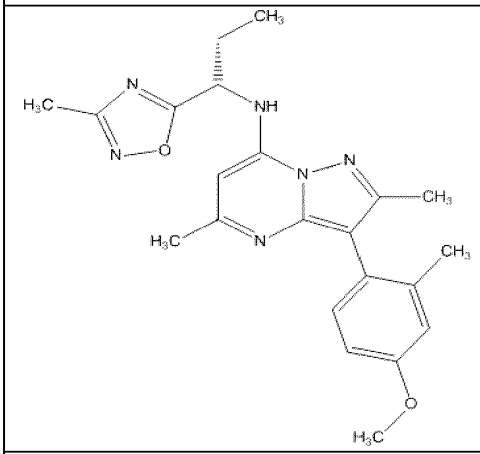
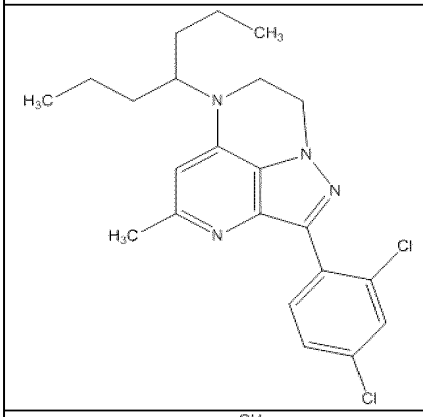
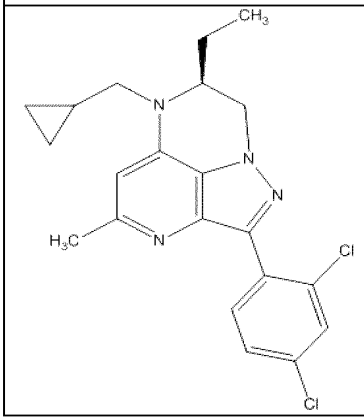
The corresponding structural formulas of some of the above-mentioned CRHR1 antagonists for use in the present invention are set out in Table 1 below:

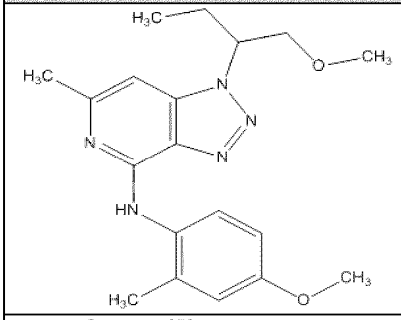
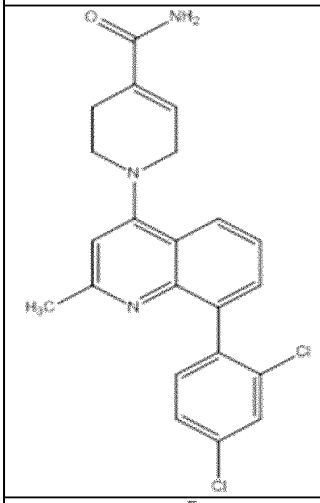
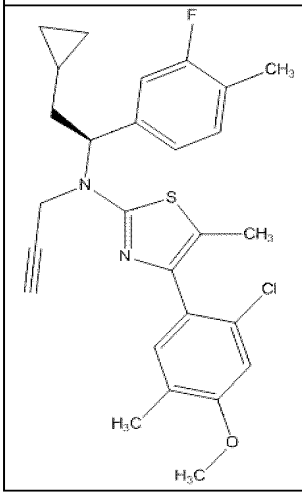
Table 1

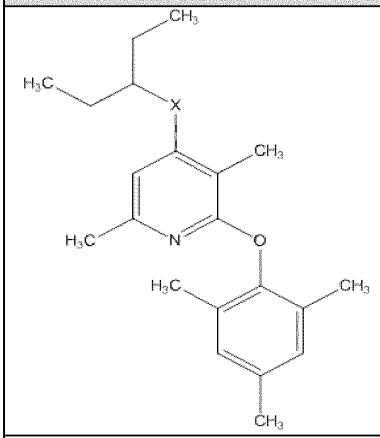
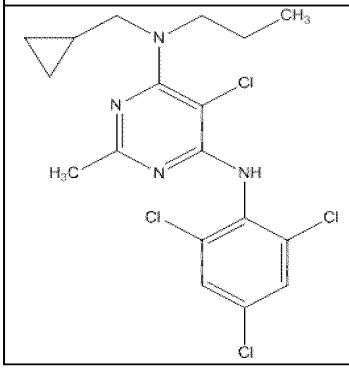
Structural formula	CRHR1 antagonist (name)
	R = H **CP154,526** R = CH_3 **Antalarmin**
	**CRA5626 / R317573 / JNJ19567470 / TAI-041**
	**GW876008 /Emicerfont**

Structural formula	CRHR1 antagonist (name)
	**DMP-696**
	**DMP-904**
	**DMP-695**
	**SC-241 / LWH-234**

Structural formula	CRHR1 antagonist (name)
	**BMS-561388**
	**BMS-562086 / Pexacerfont**
	**R121919 / NBI30775**
	**NBI30545**

Structural formula	CRHR1 antagonist (name)
	**PD-171729**
	**GSK561679 / NBI-77860 / Verucerfont**
	**SB-723620 / NBI34041**
	**NBI35965**

Structural formula	CRHR1 antagonist (name)
	**SN003**
	**CRA0450 / R278995**
	**SSR125543A**

Structural formula	CRHR1 antagonist (name)
	X = O **CP-316,311** X = NH **CP-376,395**
	**NBI-27914**

ONO-2333Ms, NBI 34101, PF-572778, GSK561579 and GSK586529 are described by Zorilla and Koob (Drug Discovery Today, 2010, 371-383) as corticotropin releasing factor receptor antagonists (corticotropin releasing factor is a synonym for CRHR1 antagonists) tested in clinical trials.

In another aspect of the invention, the above-described CRHR1 antagonists are for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having CRH overactivity, wherein CRH overactivity is detected by determining the status of a marker indicative for CRH overactivity.

In one embodiment, the marker indicative for CRH overactivity is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

The one or more biomarkers may be obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

For example, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In particular, the biomarker or set of biomarkers constituting a marker for CRH activity may be selected from one or more biomarkers of the group comprising:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

In a specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,

- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another specific embodiment, the set of biomarkers comprises at least 15, at least 20, at least 25 or all of the following biomarkers:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,

- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

For example, the set of biomarkers consists of the following biomarkers:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,

- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562,
- SNP rs10156056.

In another example, the set of biomarkers consists of the following biomarkers:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

The status of a marker indicative for CRH overactivity may be determined by a method comprising determining the status of a marker as defined herein in a nucleic acid isolated from a patient's sample, wherein the presence of indicator nucleotides as defined herein is indicative for CRH overactivity.

The term "biomarker", as used herein, relates to any nucleic acid sequence of any length, or a derivative thereof, which comprises a polymorphic variant as defined in:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,
- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,

- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

A biomarker may, for instance, be represented by a nucleic acid molecule of a length of e.g. 1 nt, 2 nt, 3 nt, 4 nt, 5 nt, 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 60 nt, 70 nt, 80 nt, 90 nt, 100 nt, 200 nt, 300 nt, 400 nt, 500 nt, 1000 nt, 2000 nt, or more or any length in between these lengths. The representing nucleic acid may be any suitable nucleic acid molecule, e.g. a DNA molecule, e.g. a genomic DNA molecule or a cDNA molecule, or a RNA molecule, or a derivative thereof. The biomarker may further be represented by translated forms of the nucleic acid, e.g. a peptide or protein as long as the polymorphic modification leads to a corresponding modification of the peptide or protein. Corresponding information may be readily available to the skilled person from databases such as the NCBI SNP repository and NCBI Genbank.

The SNPs as described herein may be present on the Watson or the Crick strand, with presence of the corresponding base. I.e. if, for example, a polymorphism is present on the Watson strand as A, it is present on the Crick strand as T, if the polymorphism is present on the Watson strand as T, it is present on the Crick strand as A, if the polymorphism is present on the Watson strand as G, it is present on the Crick strand as C, and if the polymorphism is present on the Watson strand as C, it is present on the Crick strand as G, and vice versa. Also the insertion or deletion of bases may be detected on the Watson and/or the Crick strand, with correspondence as defined above. For analytic purposes the strand identity may be defined, or fixed, or may be choose at will, e.g. in dependence on factors such the availability of binding elements, GC- content etc. Furthermore, for the sake of accuracy, the SNP may be defined on both strands (Crick and Watson) at the same time, and accordingly be analyzed.

A "polymorphic site" or “polymorphic variant” as used herein relates to the position of a polymorphism or SNP as described herein within the genome or portion of a

genome of a subject, or within a genetic element derived from the genome or portion of a genome of a subject.

The term "wildtype sequence" as used herein refers to the sequence of an allele, which does not show the CRH overactivity phenotype according to the present invention. The term may further refer to the sequence of the non phenotype-associated allele with the highest prevalence within a population, e.g. within a Caucasian population.

The term "indicator sequence" as used herein refers to the sequence of an allele, which shows an association with a CRH overactivity phenotype according to the present invention. The term "indicator nucleotide" as used herein refers to the identity of the nucleotide at the position of a SNP or polymorphic site as defined herein, associated with a CRH overactivity phenotype according to the present invention. The term may refer to a non-wildtype nucleotide at positions of SEQ ID NO: 1 to 30 as described below:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,

- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

The term "determining the status of a biomarker" or determining the status of a marker" as used herein refers to any suitable method or technique of detecting the identity of an SNP, e.g. at the positions of the biomarkers described herein. The determination method may be a sequencing technique or a technique based on complementary nucleic acid binding. The context of the indicated positions, as well as the strand may differ, e.g. from patient to patient, or from sample to sample etc.

The term "allele" or "allelic sequence" as used herein refers to a particular form of a gene or a particular nucleotide, e.g. a DNA sequence at a specific chromosomal location or locus. In certain embodiments of the present invention a SNP as defined herein may be found at or on one of two alleles in the human genome of a single subject. In further, specific embodiments, a SNP as defined herein may also be found

at or on both alleles in the human genome of a single subject. The presence of an indicator nucleotide or an indicator triplet as defined herein on both alleles may have a higher predictive value than the presence of an indicator nucleotide or an indicator triplet on one allele only, the other allele comprising a wildtype genotype. The presence or absence of indicator nucleotides or indicator triplets on one or two alleles may be connected or linked with an algorithm for predicting the a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms as described herein.

A person skilled in the art would be able to derive the exact position, nucleotide sequence, and indicator sequence from the above identified rs-nomenclature, e.g. from suitable database entries and associated information systems, e.g. the Single Nucleotide Polymorphism database (dbSNP) which is incorporated herein by reference. The information may also be retrievable in case of changes to the nomenclature, or to the surrounding sequence elements, e.g. based on history functions of a suitable database.

The term "isolated nucleic acid molecule" a used herein refers to a nucleic acid entity, e.g. DNA, RNA etc, wherein the entity is substantially free of other biological molecules, such as, proteins, lipids, carbohydrates, other nucleic acids or other material, such as cellular debris and growth media. Generally, the term "isolated" is not intended to refer to the complete absence of such material, or to the absence of water, buffers, or salts, unless they are present in amounts which substantially interfere with the methods of the present invention.

In another embodiment, the biomarker constituting a marker for CRH overactivity is REM density.

Such a marker or set of markers or combination of markers as described above may be used for predicting a treatment response to CRH antagonists in patients with depressive and/anxiety symptoms.

Exemplary embodiments for determining the status of a marker indicative for CRH overactivity are described below.

In particular, it has been found that a treatment response to CRH antagonists in patients with depressive symptoms and/or anxiety symptoms can be reliably predicted by using a machine-learning based prediction algorithm derived from the association of SNPs with values indicative for CRH overactivity.

The term "treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms" in the sense of the invention refers to a response in a patient with depressive symptoms and/or anxiety symptoms during and/or after the treatment with one or more CRHR1 antagonists compared to before the treatment. The response may range from a partial alleviation of the symptoms to a complete remission of the symptoms, indicated by the change of symptoms strength and/or frequency of relapse of individual symptoms and/or the mean change on a depression scale, e.g. as described herein. The response can occur shortly after treatment or after a certain time period. A decrease in symptom severity from pre-treatment of 25% or more is usually considered a partial alleviation of symptoms. Remission may be defined as achieving a value of 8 or less on the Hamilton Depression Rating Scale (HAM-D) or equivalent values on other rating scales named below.

A further aspect concerns the provision of an algorithm for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The method may comprise the following steps:

(a) performing a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms;

(b) determining a value indicative for CRH activity in each patient of the group, wherein a value indicative for CRH overactivity is indicative or predictive for a patient responding to a treatment with a CRH1 antagonist;

(c) identifying at least one SNP associated with a value indicative for CRH overactivity as determined in step (b);

(d) determining the algorithm by machine-learning from the association of the at least one SNP identified in step (c) with the value indicative for CRH overactivity.

In a step (a), a single nucleotide polymorphism (SNP) genotyping analysis in a group of patients with depressive symptoms and/or anxiety symptoms is performed.

A "group of patients" as used herein comprises at least two patients, such as at least 10 patients, or at least 100 patients, or at least 150 patients. Patients included in the analysis of step (a) may exhibit at least a moderate to severe depressive mode. The group of patients may comprise patients with CRH overactivity and/or patients with normal CRH activity.

The term "polymorphism" as used herein refers to a variation in the genome of individuals, including, insertions, deletions, point mutations and translocations.

The term "single nucleotide polymorphism" is well understood by the skilled person and refers to a point mutation at a certain position in the nucleotide sequence. In other words, only one nucleotide differs in a certain region.

The nucleotide, that is present in the majority of the population, is also referred to as wild-type allele or major allele. As used herein, this state is defined as "absence of a SNP".

The specific nucleotide that is present in the minority of the population is also referred as the point mutation, mutated nucleotide or minor allele. As used herein this state is defined as "presence of a SNP".

In theory, the wild-type allele could be mutated to three different nucleotides. However, the event of a mutation to a first nucleotide in the reproductive cells of an individual that gets established in a population occurs very rarely. The event that the same position is mutated to a second nucleotide and established in the population virtually never occurs and can be therefore neglected. Therefore, as used herein, a

certain nucleotide position in the genome of an individual can have two states, the wild-type state (absence of a SNP) and the mutated state (presence of a SNP).

The term "single nucleotide polymorphism (SNP) genotyping analysis" as used herein refers to a test of determining in one or several patients the presence or absence of at least one SNP, typically several SNPs, and in some embodiments all (known) SNPs the human genome, including endogenous and exogenous regions. In particular, a SNP genotyping analysis as used herein may not be limited to the CRHR1 gene or to genes of the CRH pathway. In other words, an SNP genotyping analysis as used herein can be a genome-wide screening for SNPs.

SNP genotyping analysis can be performed by methods known in the art such as microarray analysis or sequencing analysis or PCR related methods or mass spectrometry or 5'-nuclease assays or allele specific hybridization or high-throughput variants of these techniques or combinations thereof. These and other methods are known in the art. See for example Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Graham & Hill, DNA Sequencing Protocols (Methods in Molecular Biology) 2001; Schuster, Nat. Methods, 2008 and Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008. Genomewide arrays can be purchased from different suppliers such as Illumia and Affymetix.

For example, the determination of the nucleotide sequence and/or molecular structure may be carried out through allele-specific oligonucleotide (ASO)-dot blot analysis, primer extension assays, iPLEX SNP genotyping, Dynamic allele-specific hybridization (DASH) genotyping, the use of molecular beacons, tetra primer ARMS PCR, a flap endonuclease invader assay, an oligonucleotide ligase assay, PCR-single strand conformation polymorphism (SSCP) analysis, quantitative real-time PCR assay, SNP microarray based analysis, restriction enzyme fragment length polymorphism (RFLP) analysis, targeted resequencing analysis and/or whole genome sequencing analysis.

In some embodiments, any of the methods described herein comprises the determination of the haplotype for two copies of the chromosome comprising the SNPs identified herein.

A "subject's sample" as used herein may be any sample derived from any suitable part or portion of a subject's body. In some embodiments, blood or saliva samples are used. The sample used in the context of the present invention should be collected in a clinically acceptable manner, in particular in a way that nucleic acids and/or proteins are preserved.

The term “primer” may denote an oligonucleotide that acts as an initiation point of nucleotide synthesis under conditions in which synthesis of a primer extension product complementary to a nucleic acid strand is induced.

The term “probe” may denote an oligonucleotide that selectively hybridizes to a target nucleic acid under suitable conditions.

The primers and probes may be generated such that they are able to discriminate between wild-type allele or mutated allele of the position of a SNP to be analyzed. Methods for the design of sequence specific primers and probes are known in the art (see e.g. William B. Coleman, Gregory J. Tsongalis, Molecular Diagnostics: For the Clinical Laboratorian, 2007; Weiner *et al.* Genetic Variation: A Laboratory Manual, 2010).

Typically, a SNP is considered in the genotyping analysis if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 or 0.10 (MAF > 0.05 or MAF > 0.10).

For the SNP genotyping analysis a nucleic acid or DNA sample from a subject or patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample obtainable

from the patient and containing patient nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or isolated or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain nucleic acid or DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as described in the literature. However, in alternative embodiments SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sample can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In a step (b) of the method for providing a prediction algorithm, a value indicative for CRH activity in each patient is determined.

Steps (c) and (d) of the method for providing a prediction algorithm may analyze the association of the analyzed SNPs with the value indicative for CRH overactivity and/or normal CRH activity and generate an algorithm for predicting the treatment response to CRHR1 antagonists.

In an exemplary embodiment, the group of patients may be split into two sets of similar size and similar values for descriptors such as demographic descriptors or clinical descriptors. These two sets are hereinafter also referred to as "training set" and "test set".

In step (c) of the method of this exemplary embodiment, at least one SNP associated with the value indicative for CRH overactivity as determined in step (b) is identified in the training set.

Further, there can be at least two alternatives for the result provided by the prediction algorithm. First, the result may be a categorical answer whether the patient responds to CRHR1 antagonist treatment or not. Second, the prediction algorithm may provide the answer to which degree the patient responds or does not respond to the treatment. Depending on the desired result provided by the prediction algorithm the way of determining the algorithm may differ.

In the alternative that the prediction algorithm will analyze whether a patient responds or does not respond to CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as logic data variable (Boolean type; 0 vs. 1; true vs. false, high vs. low responder). Therefore, if the test performed to determine values indicative for CRH overactivity provides a data range, the patients may be dichotomized by a threshold into high vs. low responders.

In the alternative that the test will analyze to which degree the patient responds or does not respond to the CRHR1 antagonist treatment, the values indicative for CRH activity may be provided as numerical values.

Typically, SNPs that are modified in a significant percentage of the population are used in the method for providing a prediction algorithm. For example, only SNPs with a minor allele frequency (MAF) greater than 0.05 or 0.10 may be selected for further analysis. This means that only SNPs that are modified in at least 5 % or 10% of the population are selected for further analysis.

Association for all SNPs with the value indicative for CRH activity is tested by an association analysis testing the likelihood for a patient to be CRH overactive vs. CRH non-overactive in dependence of the genotype of said patient. Said association analysis may be conducted for example by an additive genetic model and/or by a logistic regression. A SNP is e.g. identified to be associated with a value indicative for CRH overactivity if the corresponding p-value is at least 1×10^{-3} or at least 1×10^{-4} or at least 1×10^{-5}. The lower the p-value the more the SNP is associated with a value indicative for CRH overactivity. Accordingly, a SNP is e.g. identified to be associated with a value indicative for normal CRH activity if the corresponding p-value is at least 1×10^{-3} or at least 1×10^{-4} or at least 1×10^{-5}.

In the step (d) of this exemplary embodiment, the algorithm for predicting a treatment response to CRHR1 antagonists may be determined by the use of SNPs in the test set by a machine learning method.

The term "algorithm for predicting" as used herein may refer to a classification function (also known as binary classification test).

The term "machine-learning" as used herein may refer to a method known to the person skilled in the art of machine learning. In particular, machine learning is concerned with the design and development of algorithms that allow computers to evolve behaviors based on empirical data, such as from sensor data or databases. It may be selected from the group consisting of artificial neural network learning, decision tree learning, support vector machine learning, Bayesian network learning, clustering, and regression analysis.

The term "reliable prediction of the treatment response to CRHR1 antagonists" as used herein may refer to a high performance of the prediction algorithm. The evaluation of the performance of the prediction algorithm may depend on the problem the algorithm is applied for. If the algorithm is used to identify patients that are likely to response to the treatment with CRHR1 antagonists the performance is usually expressed by a high accuracy and/or sensitivity and/or precision. If patients should be identified which are likely not to respond to the treatment with CRHR1 antagonists, specificity and/or negative predictive value are typical statistical measures to describe the performance of the prediction algorithm.

For optimizing the prediction performance of the algorithm, the step of determining the algorithm by a machine-learning method in a first subset of the test set and testing the prediction performance in an second independent subset of the test set may be repeated based on different numbers and groups of SNPs, until the desired prediction performance is reached.

Accuracy, sensitivity, precision, specificity and negative predictive value are exemplary statistical measure of the performance of the prediction algorithm. In the following, examples are given for determining the performance of the prediction algorithm.

As used herein, accuracy may be calculated as (number of true positives + number of true negatives) / (number of true positives + number of false positives + number of true negatives + number of false negatives), e.g. (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist + number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The accuracy of prediction may e.g. be at least 60%, at least 70%, at least 80% or at least 90%.

A used herein, sensitivity may be calculated as (true positives) / (true positives + false negatives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The sensitivity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, precision (also referred to as positive predictive value) may be calculated as (true positives) / (true positives + false positives), e.g.: (number of patients correctly diagnosed as responding to CRHR1 antagonist) / (number of patients correctly diagnosed as responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The precision of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, specificity is calculated as (true negatives) / (true negatives + false positives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as responding to CRHR1 antagonist). The specificity of prediction may be at least 60%, at least 70%, at least 80% or at least 90%.

As used herein, negative predictive value is calculated as (true negatives) / (true negatives + false negatives), e.g.: (number of patients correctly diagnosed as not responding to CRHR1 antagonist) / (number of patients correctly diagnosed as not responding to CRHR1 antagonist + number of patients wrongly diagnosed as not responding to CRHR1 antagonist). The negative predictive value may be at least 60%, at least 70%, at least 80% or at least 90%.

Other statistical measures useful for describing the performance of the prediction algorithm are geometric mean of sensitivity and specificity, geometric mean of positive predictive value and negative predictive value, F-measure and area under ROC curve, and the positive and negative likelihood ratios, the false discovery rate

and Matthews correlation coefficient. These measures and method for their determination are well known in the art.

In general, a prediction algorithm with high sensitivity may have low specificity and vice versa. The decision to select an algorithm having certain statistical characteristics such as accuracy, sensitivity or specificity may also depend on the costs associated with a treatment with a CRHR1 antagonist should the prediction be positive and/or whether such a treatment is detrimental in cases where the result is a false positive.

For a prediction whether a patient likely responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction sensitivity and/or precision of at least 55%, optionally at least 80%.

For the prediction whether it is unlikely that a patient responds to the treatment with CRHR1 antagonists the prediction algorithm may be based on a number of SNPs sufficient to achieve a prediction specificity and/or negative predictive value of at least 55%, optionally at least 80%.

For a prediction whether a patient responds to a treatment with CRHR1 antagonists or not the prediction algorithm may be based on a number of SNPs sufficient to achieve sensitivity and/or precision and/or specificity and/or negative predictive value of at least 55%, optionally at least 80%.

In one embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity or normal CRH activity in step (d) of the method for providing an algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 80% and a sensitivity of at least 70% and a specificity of at least 70%. In another embodiment, a number N of SNPs is associated with a value indicative for CRH overactivity in step (d) of the method for providing an

algorithm and/or the presence or absence of a number N of SNPs is determined in step (a) of the method for predicting a treatment response, wherein N is sufficient to provide an accuracy of at least 85% and a sensitivity of at least 80% and a specificity of at least 80%.

Typically, at least 10, at least 20, at least 25 or at least 30 SNPs are used for determination of the algorithm in step (d) of the method for providing a prediction algorithm.

The skilled person in the art knows that the use of different machine-learning methods and adapting parameters used therein can be also used for improvement of the prediction reliability. The whole statistical work-flow can be automated by a computer.

Another aspect is a method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, wherein the method may comprise the following steps:

(a) determining in a nucleic acid sample obtained from a patient the presence or absence of at least one single nucleotide polymorphism (SNP) associated with a value indicative for CRH overactivity;

(b) predicting the treatment response to CRHR1 antagonists by linking the prediction algorithm provided by the method described above with the presence or absence of the at least one SNP determined in step (a).

"Linking an algorithm for predicting a treatment response to CRHR1 antagonists in patients having depressive symptoms and/or anxiety symptoms with the presence or absence of the at least one SNP" as used herein may refer to using such an algorithm to predict the treatment response based on the determined presence or absence of the at least one SNP, e.g. by integrating the at least one SNP determined in step (a) of the above method by the algorithm.

In one embodiment the method comprises a further step of obtaining a nucleic acid

sample from a patient preceding the step of SNP determination.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, step (a) comprises determining at least one of the SNPs, optionally all of the SNPs which were associated with a value indicative for CRH overactivity when determining the algorithm by machine-learning from this association.

Typically, a SNP is considered in the genotyping analysis of step (a) of the method of prediction if it occurs in a certain percentage in the population, for example in at least 5 % or at least 10% of the population. In other words, the minor allele frequency (MAF) is larger than 0.05 (MAF > 0.05) or 0.10 (MAF > 0.10).

For the SNP genotyping analysis of step (a) of the method of prediction, a nucleic acid or a DNA sample from a patient may be used. The nucleic acid or DNA sample can be a blood sample, a hair sample, a skin sample or a salvia sample of the patient. Any other sample of the patient containing nucleic acid or DNA can also be used. The sample can be collected from the patient by any method known in the art. For example, a blood sample can be taken from a patient by use of a sterile needle. The collection of salvia out of the mouth and throat of the patient can be performed by use of a sterile cotton bud or by flushing said area and collecting the flushing solution.

Usually, the nucleic acid or DNA is extracted or purified from the sample prior to SNP genotyping analysis. Any method known in the art may be used for DNA extraction or purification. Suitable methods comprise *inter alia* steps such as centrifugation steps, precipitation steps, chromatography steps, dialyzing steps, heating steps, cooling steps and/or denaturation steps. For some embodiments, a certain DNA content in the sample may be reached. Nucleic acid or DNA content can be measured for example via UV spectrometry as known in art. However, the SNP genotyping analysis may also be performed by using a non-extracted or non-purified sample.

Nucleic acid or DNA amplification may also be useful prior to the SNP analysis step. Any method known in the art can be used for DNA amplification. The sampled can thus be provided in a concentration and solution appropriate for the SNP analysis.

The analyzed SNPs may be represented by values 0, 1 or 2. The value "0" may indicate that the SNP is present on none of the two homologous chromosomes. The value "1" may indicate that the SNP is present on one of the two homologous chromosomes. The value "2" may indicate that the SNP is present on both homologous chromosomes. Homologous chromosomes correspond to each other in terms of chromosome length, gene loci and staining pattern. One is inherited from the mother, the other is inherited from the father.

In order to determine SNPs, SNP-specific primers and/or probes, a primer extension reaction, SNP microarrays, DNA-sequencing may be used. These reagents and methods are routinely used in the art (see for example Chen, PCR Cloning Protocols (Methods in Molecular Biology) 2002; Schuster, Nat. Methods, 2008, Rampal, DNA Arrays: Methods and Protocols (Methods in Molecular Biology) 2010; Brenner, Nat. Biotech., 2000; Mardis, Annu Rev Genomics Hum Genet., 2008). For example, MALDI-TOF (matrix-assisted laser desorption ionization time of flight) mass spectrometry on the Sequenom platform (San Diego, USA) may be used to genotype the selected variants. For primer selection, multiplexing and assay design, and the mass-extension for producing primer extension products the MassARRAY Assay Designer software may be used using the sequences presented in table 2 as input. The MassARRAY Typer 3.4 software may be used for genotype calling. Any other reagent or method known to the person skilled in the art may be used in order to detect the SNPs in an individual.

In one embodiment, at least one SNP determined in step (a) and used for the prediction algorithm of step (b) is a SNP selected from the group consisting of SNPs as shown in table 2 and an SNP in strong linkage disequilibrium with any of the SNPs shown in table 2.

Table 2: SNPs (together with flanking sequences) which may be used to predict the response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms. The position of the SNP is indicated in bold as **[wild-type allele/mutated allele]**.

SNP_ID	SEQUENCE
RS6437726 SEQ ID NO. 1	CAAGAAAGAGAGTAATAAAAATAACCACAATGAGGGCTCTCATTAATACT GGATCTTATGGAAACCAATTGTTCAGTCCCTCAACAAAAGACCAGATGG GCAGGAAGCTAAATATACACCATGCACTAAACATTATGAGTATCATAGTT TACAAGTCAAAGGGGGCTCTATTGAAGATAGTTCTATTTTCCCTCTATAT T**[A/G]**TCTGCTAGACAATACCTGATAACATTATCCAAGTAAATGACAACTT GATAAATAGTAATTTCCAATGGTGAACAGAGGTGACATTTCCTCATTACA AAAATATTTTCTTTGGCAGATGAGATTAACTGAATAAGAAATCCACTGAC ACTGAAATCACAGAGCCAAATTCCCTATCACAGCACTTATCACATTGCGT TAGG
RS1986684 SEQ ID NO. 2	TTCCTTGTAGCGGGGAGAGAGACTCAGGGAAGGCAGGGTGATACCTGA GTTGGGGCTTAAAGCAAGGTAGGGTGTGTGTGGTGATGGCAAAATAGG TAGGAAGACAGCACGGGCAAAGTCCTGGAGGCAAGGACAGAAAGAGGA AGTGGCAGGAAGTGAGGCTGGGGAAATGAGTAGGGGTCAATCATGATG TTTCTGGT**[A/G]**TAGGGAAGAGTTTGGAATGCATCCTCTAGGCCATACGC CATTGGGGGCTTTTAAGAAAGACAGTGATGTTGGTTTGATTTGCATTTTA TATAGACTTTTCTGGCAGCTGAGAGGAAGGTGGTTTTGAGAATCACAAA GCTGCGGGAAGATCAGTCAGGAGGGTTCTAGAATAATCCAGGCAAGAG CTGATGGGGACTGAG
RS7380830 SEQ ID NO. 3	ACAGGGGTGGCTACTCTTTCTCCAGAAATAGGTGTCCTGTGGGGCATTT TGAAGTAGAATGTTGATAGTTGCTTTCAATTTTAGACTGGTAAATAAGAAT TGGGCATTTGAATTTCAATATACTCACTGTGTAACTGTTATTGAGTATGCT TTAAGTGACCTATAATACTGCTTCATTTAACTTTATTGTCCTAATAACT**[C/T]**TCTTAGAGTGACAATAACTTAGGTTAGCCACTTGCCTAGGGTTCTGAA ACCAAGTAAATGGTGGAGCTGGAATTGC**T**GTTCTTGTCAGTCATTAGACT AGATCGGTTTTCTTCTTCCTACAAATTTTATATACTAAAAAATTTTGAAAAA AGACATTTT**T**TCTTTGGGAAAAATAGGGAATGTCAGATCCCTTTGGAGATG
RS3903768 SEQ ID NO. 4	CTCGCAGCAACCAAGCCTGCCCAAGCCGGGGAAACCTGGGGAGCAAAC CTTCACCTGCACTGTACATCAGAGACCAGTTGGCCCTATTTTGGCTCCT GTGGACAGGTAAGTATCCCTTTTGACTCATCCCCCAAATATCAGGTGAG CCAGGAAAATAAGGCCTTTGGCTTAGACAGTCAATTCAAAGTCTGCCAT AGCAT**[A/C]**CCTAATTACATCCCTATTGCCCCTTTTCTAGGTCGTTTCTCC TCTAACACGATTTTATTTTTCTGTCAGCCATTTTATTTTATTTCTCACCTTG AAATATATGTTTTCTTTGCAGTTTTTGCTTTGGCTTCCTGCTAACTCTATT TGGGCAATTGTTTAAGGCTGAACACTTGGTTATGAGAGGTACCCTGTTG TGTTGA
RS7325978 SEQ ID NO. 5	TCATCAAGTCTCCTTTTTCTCTAGGAAAAATAACATTGTCAAGGTTATTAA CAGTCAATAAGCTGTCATAGGCTCAGCATGGATGGGGATATTGGGTTTC CTTGTGCTTATATGAAAGATGGGAAAATCCGAAGTTCTTTTCACCCTGAT ATGGAAAATACCCAACATGAGGAGAAGCAGCAGCTATATGATTCTGAGC A**[C/T]**AGAATGGGAGTAAGAATAGGGTCATGCTGTACTGATTATCTGCTA ATAAAATGCAAAAGTGTTAGGTAATTTCATCAATATCCAGTTAATACTAAT ATAGTTAATATTTCATGACTGGGTAATATTTTATAATGATAAATATTTTTAT AGATCTTAGCTCTTTTTATTCTCATATCAACTGTATGAAATCAGTGATTGG T

SNP_ID	SEQUENCE
RS13585 SEQ ID NO. 6	CTGGGGACCTCAGGGAGAGGTACGCAGGTTGCCATGGCTGCGTCTGCA GTCCACCTGCCTTTCCACGCCAGGGAGTCAGTGATGTGGAGCCCCCTG GGCCCCAGTGGAAGCAGCGATCAGACTATGTGTCCTTGAAATAATGTTT ATTCCACGCTGTCCCGACAGCCCCCTCTGCAGGTCCCCT**[C/T]**GGTGTA CTCTGAGGTGGGAAACCCTCCCTGGGGGCGGTGAAGGGGAACTCGGG CCACCCCACCAGCCAGCAGATGCTCCAGCAGCCAGAGCCCCAGCCTGG AGCTGAGGCTCTTCCTGGGGCTCGCCGGGCCCCTGCAGGCTTTTCGGA CCCTCAGCCAGCCCGGCTTCCTCTGCTTTGGGCAGCAGCAAGCTGGCC CTT
RS9368373 SEQ ID NO. 7	TTCCTGTGCCTCAGCTCCTCTGTAGAATGGTGCTGGCAATACAGTTTGC CTCATTGGGCTCTTGTAAGCTTTAAATAGGTTATTATACATAAAGAGCTA ATAGTGATGCCTGTAGCCGTTGTCTAAGTGCTAGCTCTGATGATGGTGA CAAAGAAGTAATAGCAATCAGTGGTTTAGATTAAACCATTTTAGGCATAA AC**[C/**T]GTTCTGCTAGAATCCAAGGGGAGATTTTTTCCCATCAAGGAGAC ATAGCTTGTTGGGAAGATAAGACATACCCAATTGCAGAAGTAATTAATTA ATTCTTTTTTTTTTTTTTTTTTTTTTTTTTGCGATGGAGTTTCGCTCTTGTT GCCCAGGCTGGAGTGCAATAGCATGATCTCGGCTCACCACAACCTCTG CCTCCT
RS10935354 SEQ ID NO. 8	ATAGGCCCTATACAGCTCTCAATTTCTTTAATCAATCTTCCTAGCAGCCC GTGAGAAATATTACTGTCTTCAGCTTCCTAAAGGAGAAAACAGAGGCCT GGAGGGATTAAAAGACTTTTCTAAGATTTTAGAGGGCATGTTAGGGTTCA GGCCCAGGGCTGTCTAACCCAAGGCCTAATTCCTTCTATTACATCCATC AT**[A/G]**CATGAGTGAGCACTGGGCATGAGGATACGTCAGTGAAAGGGGC CCTGTAACATGGACCTTACATTTTGGCTGGGGGAGACAGGCAATGAATA CATAGGACCATGTTGGGAAGTGCTAAGTACTCTGATGATAACACAGCAG GGTGAGGTGACAGAGGTCTAGGGAGAGTGGTGTTCAGCAAAAACTTCT CTGGGGAGAGA
RS8095703 SEQ ID NO. 9	AAAATTTACCAGGTTTAAAAAAAAAAAAACTCAAATGATATTTCAGAAACC TACCCCTTTCAAAACAAGGAGGAGAAAAATCTTCTCCACAAAAGCACATA TTGAAAAAATATTTTGGGGGCAAGGCCTGAAAGGGTTGGCAGTGTGCAG TTCTGTTATTATTCCCGTGGCCATTTTATGGGCCTCAGCAAAACACTGGG **[A/G]**TCATTATCTGTCTTCTGGTTACTCCAGGAGAGCTAGCCATCACAAC CCAATGGAAGAGACTTCAGAGAAACCCACACAGGCACCAGAAGTCCTTC CCTTTCATCTGCCACTGTGGGGTTTTGTCCTCATCTATTACAATGTTGTC CAATCTCAGACTGCATTCAGAACAAAGGCTCTCAGACTGAGGATGAGTT CTTGGA
RS10206851 SEQ ID NO. 10	CCAAATAATTGTTATTGTTGTTTTAACATGGCAATCACGTTATTTGCCATA TGTGAAAAAGAATATTTAAAATGCTTTTTAAAACTATGTATGTAAAAGAAT GTTTAAATTGTTTTAAAAATATGTTATATCTACCTTGGCACCATCCTTGCT GTTGAGAAATGACTTTTACCTGCTTACTTAGAAGGAAATGTCAGAAG**[C/T]**AGAAGTACATTTGAATACGATTATTTGAAAGCTTCATCCATTTTTCAAAG AATGTATACAGTAACACTAAATAGAAAGCATAGTTTATCAACTCTTCACTA AGAACAGTCTAGCAAGTATATCAGAGTGGCTGTGGTTCCAGTTGGACTA ACCTAATCATTTATGAAAAGGTGATAATAAGCTTGGACCAAGAGCACCCA
RS9542977 SEQ ID NO. 11	CAGATGTTATGTGAAACTCTGGAGAAATAGTAGCAAGCAAGACTCACAT GCCTCCTGCCCTCACAGAGCTCCATGATCTGGTGAAAGTGCCAGATATT TAAACCCATGGATGTGTGCACACAAAATAACAATTCTCTCAAGCGTTGTG AAGAAAAGTCACAGAGCACTACAAAAGCATGTAAGAGTGAGGCAAAACC TAT**[C/T]**GTGTTAGGACAGGGAAGGCTTCTGTGAGCTAACCTGAAGGAT GAGTAGGGGTGAGCCAGATGAAAAGGCGAGAGAAAAACATTCTGAGCA GAGACTGCCACTGAGTGCATCCCAGTTTTCCCAACATCTTAACACTGTAT AATGACTACACTGGATTTTCTTCATCCTGGATCCATGGTTAGACATGTTA ATATGCCTTC

SNP_ID	SEQUENCE
RS4942879 SEQ ID NO. 12	CCCAGTCTGTGGTATTTTTTTATAGCAGCACAAACAGACTAACACAAGAG GTGGATAGGATTTGCGAGCATGGACCTTGGAGGTTTGTGGCCTCAATTT AAAGTGAGTACATTCACCCAGCTGGTGTTTTTCTCTTGCTGCTTGGGCA CAGAGATGGAGTAAATGGGTCTAATCAAGGATAAAGGGAGAGCCAAAGA GAT**[A/G]**GTAATATTTGAAAGGAAGTGTTTTTAATGATGTGCCATGTAATC TGAGCTGGGTCAGGAATGAAGTGAAAAACTAAGAGATGATGGATGATGA TAGGGGCTGTGAAAGGAAAACAAATCTTGGGGCCCCCAAATCACTAAGC TAAAGGAGAAAGTCAAGCTGGGAACTGTTTAGGGCAATCCTGCCTCCCA TTTTATTCA
RS9542954 SEQ ID NO. 13	TATTACTGCTGAGAAAACTGGGTTTGATAAACTAAAGATGCCCATGTATA TCAGTCATGCTCCTGGTGAGAACAGGTGGCTCACTGCATAATGAGAGGA ATATTCAATTAACTATTTACAAAGCTATGGATGACATGTAGGGAAGCCAC AGAGAGAGTACAGTATCTAGAGCTAGTAAGAGTAGAAGGCCATCACTGT CC**[A/C]**CAGGCCTAAAGGAGGTAGAGCAGTCAAAGGAAACAAGAGACAA GGGAGGCTGCGAGGACAGGGCCACCTGGCAGAGCCATAACCTTAAACT AGGTAGTCACTTCTTGGCAACTCTGCAGGTAGGGAGCCAACCTCACTTT TAACCCTCCCTCTGATGCCCAGCTGGTTTACCCCATTGGTGAAAATCAG TGGGTGAGGGA
RS1593478 SEQ ID NO. 14	CATGAAAAGATACTTAACATTGTAACATCTTTGCATTAGGGAACTGCAAA TCAAAATCATAACAAAATAGTACTGCATGCTCATTAGGATGACTATAATC CAAAAGAATAAAAAAGAAAATAACAGGTGTTGGTAGGGATACAGATATAG AGAAACTGGAGCTCTCATGCCTTGCTGGGGGGCATGTAAAATGATTCTG C**[C/T]**GCTTTGGAAAACAGTTTGGTGGTTCCTCAAAAAGTTAAACATATAA TCCAACAATTCCACCCAAAAGAATTGAAAGCAGGGTCTAGTACACCAAC GTTCATAGCAGCTTTATTCACATCAAGCCAAAGGTGGAAGCAGCCCAAA TGTCTACTGATGGATGAGTTGATACACAAAATGTGGTATATATATGCAAT GGAATA
RS9542951 SEQ ID NO. 15	GCCACTTGAATGCCCCAAAATGGAGAGA**T**GGGCGTGGGAAGAGAAAGA CACCTCAGCAACACAGAGCTGAGAAAACACTGTGAGTTTTATTTAATTCC TACTTACCGTTATTTTGCATAGTAAACAAAAGGGATATTTTTGAAAATCCC TTTGGATAATTTCTGCCACCTAAAATTCTGAGCATTTTGACTCACTGCCTT **[A/G]**TAAAAAGAATCAATTAATTGAATAAGAGAAGGGATTCTCCCCTGAT CTTTTCAAGAATCCTTAAAAGGCACATTTCTCACTAAGGATCTTGAAAGT GTATTTCTAGCCAATCCCAGGAGTCACTGCTCAGAGATTTACATTTCACA AATGTAATCAACAGCCTAAGCAGAATATTGACGTTTGGACTGCAGAGCT CTGCT
RS2188534 SEQ ID NO. 16	AGGGTCCCCAAATATTTCCATTTGAGATGACAAAGTGCTCTTCAGTCATT TAGCTTACTCTTCAGTTCAGATGACTTATCATCTTGATTTCAGAGAGTTCA TATATGTCTGTTTTAAAAAACTGGTTCAAAAAGTCTGAAGTTACGAAACTA AACCAAATATGCATTACTCTCATGTCAAATTACAAGCTCTTAGCTGC**[G/T]** GGGATTTTTTCACATGCAGCCTGGAGCCCTTGAAAACCTCTGTTTTCTGT TAGACTCTCCAGGGTACACAGAAGTTGCCTCATTATTTTAGTTAATGGTG ACTGCAAATAAGCCCCCCAAGTCATTTAACTATGTGCTTACCACTGCTTT AAAAGAACCCCAAGTTAGGTCCTCATGTAGGTAAAGGAGCTCCCTTCAC A
RS12524124 SEQ ID NO. 17	ACTTGGGCCCAAAGGCATTCAACTAGAAAGCTGGTAATAATAACAGCGA CAGTTTATTGAGTCTTAGTGTTTCTGAGAACTTTTCTAAGTACTTTACACA TATTAAATTTTTAAATCTTCACATTAGTCC**T**GTGAGGAAGGTACTATTGTT ATGTCTGTATTACCCATGGGGATACTGACGCACAAAGAAGTCAAGTAAT**[A/G]**TATTTAAGATTCTAGTAAGTGCAGAGCCCAGGTGCATGCAGTGCCT GGGCTCTGCCACCCATGCAGTGCTGACTAGGGCTTCCACCCATGGATTT TTTTTTTTTTTTTTTTTTTTTGAGACAGAGTTTCGCTCTTGTTGCCCAGGC TGGAGTGCAATGGCATGATCTCGGCTCACCACAACCTCCGCCTCTCGG GTTCAA

SNP_ID	SEQUENCE
RS4352629 SEQ ID NO. 18	CCCATAATAATGAAGGATTGGACCTGATAATCTATCAGGTACATTTTAGC CTGAAATTTATTTGTACACACGCACAAACACAGACATGTGCACACACACA TACACATATATATATAACATTTATAAATTTTAAAACATAAAGCTATACTAGA AATGAAAGCTTATATATTGAACTGCCCCACCTTTCTATTTGCAGCCAG**[C/ T]**TACCACCCCAGTCTAATGTTTCACTTTATATAAATTCATTTATTCTTTTA CTCATTTCAAATATATGATGATGTAACTATAAAATCAACATTTAGTCACTC TGAATAACCCAAAATAGCAAATAATTTAAAAATCACTTCCACTTGACTTTA GAATCTATTACATGCATTGTTTTTCCAGAAAATTTACCTCATAATTAT
RS7448716 SEQ ID NO. 19	CTACTTATATGATTAGAGAACAAGAATACTAGGGGGAAAATCAGCATGCA TATAATCTAAGAAATTGTCATTATAATTTTAAAATCCTTTGCAAAATCAGTA AATATGAGTTTAACTTATATAATGATACACACACACACTGATATGATGCTT TATTGTCTAAACACTGGCTGCTTGTGGAGACGTATTCTGGTAACAAA**[A/G]**AATATAGCATCTTAAAATTGATGCTAGCATTGTATATCCAAATAGAGAGT AAATGCAACCAGAATATTTTTTATATGTTTAACATTGTAGTGTTGCTGACA TCATTATATATTTGGTTATGTTAATCTCAAAATGCACAATATAGCTGTATG ATCTGTATAATGCAAAAAAATGTAGAGCTTCATTTTGATATTTATTAT
RS11873533 SEQ ID NO. 20	CTGGAAGGGAACAATGGAAGAGGTGCATTAGTCACATTCCAAAATGCAG GAAGCAATAACATGTGGCACTATTGTCATTTATGTAGCACCCTAAATACT GGGACAAATGACATAGATGCCCTTCTGTGATTACTAAACTCCCCCACAG TGTCTCAGAAGGAAGAGCTTTTGACAGGAAATCATCAAGATCTGATGAC ATT**[A/C]**GAGAGCAATTAACATTCTCTTCAACCATGAACTAATTGCCTCAT TCACATTTTTCTAGCCATCCTAGGAAGCAGATAATAAGCAGCAATTGTCC TGCCCAGGAATTCTGACTTGTGTAATTTGTAAAGCTTTTCTTTGTATCTAT TTCTTTCCTGTGGCCATCTTTTTGTTTTTGGACTGTTTGGTAACAGTAAGT GGGT
RS10062658 SEQ ID NO. 21	ATCATTCAGTATTAAGAGAGAAATGAATACATTTTCAGATATACAAGAATT CAGTTTACCTCCCACAGAATCTCTGAAAAAAATATTAGATTACTATAGTTA AAAAGGAAAATAAAATAAGTCCTGTTAGAAATAATTGGTAAAAAAGCAAA GGTGATGAAAACTTATTGAAATATATTATTAAAGTAATTGTTAAAAAT**[A/G]** TACACTAAATCTAGAATATATAAATGTAGCAGTTGTTAAGGGGAAGGGGA AATAGAAGTGGAAGAAAATGAACATTAGAACAAATGTTTAGCAGTGGGAT TATTTTATTGGAAGTCTAATGTAAGAAGTATATTCTCCAGGGAGGTATTT CAAGGACATATGAATAGTAAAGGGATAATAAAACAACTCTATAAGGTAGT
RS12547917 SEQ ID NO. 22	CACACACAACGCTGGGCCCAGTAAATAAGTTTTGTTTTTTCCCAGGGAA AAGTTGAACAACAATGGTGAGACCAGGAAGGCTCTCCGTTCACAGGAAA TACTGTGTCACCGCTCGGCCGCAGGCTGTGTGAGGTCACGGGCGACGC TCGGGTCACGTGTGGCGGCTCCTGTTCACAGTGCCGTGTGTGATAAACT GGGAC**[C/**T]TTCTGGTGAGGGGAGACTGGCGGGGGGTGGGGAGGGCA AGGAGTGGGAAAGTCGCCTATAAATGTTTAACAAAAGATCCGCAATGGG AACAGGAACTTGCATTCTTTCTTTCAATGGACAAAGCTTCCACATCAAGA TACGCTTGTGTGCTGGGACCAAATGCCACAGTGCGGCGAAACTCGTGA GCACAAGTCCTGCGT
RS1038268 SEQ ID NO. 23	ACAACAGGGTATCCTAGCCCAGCAAAATTGACTCATAAATTTAATGATCA CGCAATTGGTAATTCTAAATCCAGTCAGAAGTCTACATTCTGTGTCCACA GTGTCATGTCTAGATGTTGGTCCAGTCTCCCATGGACTGTGCCTTGTTAT TTGTTTTCTCTTTGCTAAGCCACATCCCCTGAGGGCTCTGTTTATGCTCA**[C/T]**TGCAAAATCTTTGACTTTTTAACTTACTGGGCATATTGTCTTCCTACT TTTGTTCTCTTCTGTTATTTTATTTACTTGACTCTGACATGTCTCATTCCC

SNP_ID	SEQUENCE
RS2375811 SEQ ID NO. 24	TTTCAATGGGACTGGTTGGACAGTGGGTGCAGCCCATGAAGGGCAAGC CAAAGCAGGCCGGGGCATCACCTCACCCGGGAAGCACAAGGGGTCAG GCGATTTCTCTTTCCTAGTCAAGGGAAGCCATGGCAGACTGCACCTGGA AAAACGAGACACTTCCACCCAAATACTGCGTTTTTCGCAAGGTCTTAGCA ACTAAC**[A/G]**GACAAGGAGATTCTCTCCCGTGCCTGGCTCGGCTGGTCC CACACCCACGGTGACTTGTTCACTGCTAGCACAGCAGTTTGAGATCGAA CTACGAGGCAACAACCTGGCTAAGGGAGGGGCATCTGCCATTGCTGAG GCTTGAGTAGGTAAACAAAGTGGCCAGGAAGCTCGAACTGGGTGGAGC CCACTGCAGCTTAGCA
RS1352671 SEQ ID NO. 25	ACTTTAGGGACTTTGAGTGATGGACAACCCCCTATCAGATATCATCAGC CTGAAACATCCTTATCTTGGCATTAAATTAGAAGGAACCCCAGACCCTGC GTACCAGAATTGTTAGAATCACAGTCTCAGTAAAGAACCAACTCCTGATC ACTTCTCTAAAGGAAAGTTCTAGAAGTCTGCACACTCTGCAGTCACTTTC A**[A/C]**TTCTATCCAAGTGTACACTTAGAACTCTAGAAAACACTACGGACA GTCTTCAGCCAGGTAAAGCCTAAAACCAGCAAAGAACAGGGAGAGTGA GGGA
RS364331 SEQ ID NO. 26	CGGATTATCACAGTTCTCAAAAGAGGAGTATGCATTTGCTTGCTCCAATT CCTCTTCTTCTACACTCTCTTAAGCATTCCTCAACCAGTCTAATATCTCAT AGTTCCCCAAAACTGCTCTGTTCAAGACCATTAGTAAGATCTTTGATGTT AATCTGTGGACCGTATCTCTGTCCTTATTTTACTTGAAGCCCAACAGCA**[A/C]**ATAAAAAAGTTGTTCTCCTCTCCTCCCTGCTACACTTTCCTTATGTG GCTTGCTGGGCTCCTCAGTCCCCTGTGAAAAACTCTGACATGGAGATAC TGCAGACCAGTAGAAGGGCTGGGCAGACACTATACAGAAACAGTATGC CCTACATGCTCCTTGGCTAAATCTCTAGAATTTTTTTCAGAACTCATCCA CAAATT
RS1924949 SEQ ID NO. 27	ATTTTATCTCATTTACTTATTAAATCAAACCAATATTTTATGAAGTGATTCC AGTATTGGAATAAAAATGTAATTCTTTAATCATTAAAAAATCTTTATGAATA CCTTACATCAACTGTAGGGGACCAACCAGGGAAAAGCAGGGAGACTTG TAGAATCTACACCTCCAGAACAACCGACCTCCATCTTCTGGACAACTC**[A/ G]**TCTTCTAAAGTGCAGGACAGACTAGTTGGGGGAGAAAGGAGGAAATG AAAGAGATAGACTAAAAGGGAGGGAGAGAACAGATATTTTTTAAGTACC TGTTATGTTCTGGATACAGCACAGAGTACATTGTATCTATTATTATAAGG CATAAAGAAAGATTTCTCAGGTTTTTGGAGTCAGATTGCAATATAAAATA ATAG
RS11025990 SEQ ID NO. 28	TAACTTCAAATTGTTTTGCAAAATCTCTGTCATAAAAATGCTTACCAACAA ATACTGATACTAAATTTAGATGTGGGGGTATTAGTTATAATCCTGAAGTG GGAGGGGGAACTTCTTAATTCCAATTTAGTTCTAAGAGAAGGAAGAGTA TTTAGGCCCAGAGAAGGTTACGCTTAAAGGTCTGATAGTGTTTTCTTTGA **[A/G]**AAATATGTCTCAAACTAGAGAATAAAACTAATTATCTCATCTAAGTT ACCTAGAGACATTTATGCTCATCAGTTTGATAAAGGACTGCAAGTAGACA CAGAAGCTGTATTTTCAGTCTTGAACCCAGCAATAGTACATTAACAAGAT TGGGGCAAGGCAAAGGGACTTTTGTGGCACAAGATACAATATATGGATT GCGT
RS3758562 SEQ ID NO. 29	CTCTTCAAAGGCCTTTGCCCTTGGGTACCACAGGTTCTGAGACAAGAGG GCTATGGAGAGCCCCCATTATAGCTGGAGCCTCCTGCCCTGCCCAAAG GTGTGACTTGAAGGGTGGAATTTCAGGCAGCGTGGCTCGCCCCAGGGA GGCAAAGAGGCCAGGGGAATCTTCAAAGGCCCTGGGCTCATCCCAGCT AGGAGGC**[A/G]**GGCACAGTCATAACCCTAATCCAGTGAACTCAGCCCTC ATCCTGACTCTCATGGTATTCTGTCCCAGGGAGCCTCTTTCCAGCTTTCT TAGAAGCTTTAATGTCAGCACTTGCAGGGCCTTAGAAACTGCACGCTAC CTCTTCATTTCATACATGAGGAAACTGAGGCCCAGGGTGGACACAGGGC TGCCCAGCGAGTTA

SNP_ID	SEQUENCE
RS10156056 SEQ ID NO. 30	ATTATAAAGCAAAGCACTAACCTCATAGAATACCTGAGTCAAGTTCCCTG TGTTCTCATTTTCTAGCCTCTTCTACCAGACACTATGAAAAATAACAGCC CCATCTCTCCAGAAAATCTTAGGAGATATAGGCGTGCTGAATTTAAGGT GTCTGTGGCACATGCAAGTGGATCAGCCACTGGGCTGTCCAGAATGCA AGA**[C/G]**AGAACTCAGAGTTGGGGACATAAACTTGGCAGTCATCTGTGTA AAAGAGAAAAGGTAGGTAAAGTCCCACAAGGATGGGTTGGCCTACAGAA GGCACAGAGAGAAGAGAGCCTGGTTTAGCATGGGCTACGATCAGAGTC CCTGGGTTCAAATCTTGGCTCCACCCATTTCTATCTGGTTGCTCTAGGG CATGTTACCTA

Polymorphisms in linkage disequilibrium with a SNP of table 2 can be identified by by methods known in the art. For example, Develin and Risch (Genomics, 1995) provide guidance for determining the parameter delta (also referred to as the "r") as a standard measure of the disequilibrium. Gabriel *et al.* (Science, 2002) provides instructions for finding the maximal r^2 value in populations for disease gene mapping. Further, Carlson *et al.* (Am. J. Hum. Genet. (2003) disclose methods for selecting and analyzing polymorphisms based on linkage disequilibrium for disease gene association mapping. Stoyanovich and Pe'er (Bioinformatics, 2008) show that polymorphisms in linkage disequilibrium with indentified SNPs have virtually identical response profiles. Currently, several databases provide datasets that can be searched for polymorphisms in strong linkage disequilibrium, which can be accessed by the following addresses: http://1000.genomes.org, http://www.hapmap.org, http://www.broadinsitute.org/mpg/snap. An example workflow for determining SNPs linkage disequilibrium to a specific SNP is outlined in Uhr *et al.* (Neuron, 2008).

SNP in strong linkage disequilibrium as used herein means that the SNP is in linkage disequilibrium with an r^2 higher than 0.7 or higher than 0.8 in the tested population or an ethnically close reference population with the identified SNP.

In another embodiment, at least 20, optionally at least 25 or at least 30 SNPs selected from the group of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). For example, all intergenic SNPs of table 2 are determined in step (a) and integrated by the prediction algorithm in step (b). In another exemplary embodiment, all SNPs selected from the group of table 2 are determined in step (a)

and integrated by the prediction algorithm of step (b).

Typically, in step (a) of the method of predicting a treatment response to CRHR1 antagonists, the presence or absence of those SNPs is determined which were identified to be associated with values indicative for normal CRH activity or CRH overactivity and were thus considered when determining the prediction algorithm by machine-learning as described above.

In one embodiment of the method for predicting a treatment response to CRHR1 antagonists in patients with depressive symptoms and/or anxiety symptoms, the method as described above may be accompanied by analyzing the rapid-eye-movement (REM) sleep, e.g. during night sleep of a patient in a sleep EEG.

In other embodiments, an increase in REM sleep may serve as a biomarker to identify patients who would benefit from treatment with a CRHR1 antagonist.

REM sleep typically comprises a characteristic coincidence of nearly complete muscle atonia, a waking-like pattern of brain oscillations and rapid eye movements (REMs). The amount of REMs during consecutive REM sleep episodes is usually increasing throughout the night. Single and short REMs with low amplitude can be characteristic for initial parts of REM sleep. The amount of REMs, in particular within the first REM sleep episode, can be of clinical relevance. Recent clinical and animal data supports the correlation of REM density with an increased CRH activity. For example, Kimura et al. (Mol. Psychiatry, 2010) showed that mice overexpressing CRH in the forebrain exhibit constantly increased rapid eye movement (REM) sleep compared to wildtype mice. In addition, it could be shown that treatment with the CRHR1 antagonist DMP696 could reverse the REM enhancement.

Further, the SNP analysis and REM density analysis as described herein may be combined for predicting the response of patients with depressive symptoms and/or anxiety symptoms to treatment with a CRHR1 antagonist. The REM analysis may be carried out before, concomitant or after the SNP analysis. For example, the REM

density analysis may be carried out on persons that where identified by the SNP analysis as CRH hyperdrive patients.

The recording of a "sleep-EEG" (also referred to "polysomatic recordings") may comprise electroencephalography (EEG), vertical and horizontal elecrooculography (EOG), electromyography (EMG) and/or electrocardiography (ECG). In EOG, muscle activities of right and left eye may be recorded by electrooculograms (one or typically two channels) in order to visualize the phasic components of REM sleep.

"REM analysis" or "analyzing the rapid-eye-movement (REM)" may refer to a method comprising recoding of muscle activities of right and left eye by EOG and then analyzing the electrooculogram. The recognition of REM in the electrooculogram may be done manually (for example by standard guidelines Rechtschaffen and Kales, 1968, Bethesda, MD: National Institute of Neurological Diseases and Blindness).

The invention is further described in the following example which is solely for the purpose of illustrating specific embodiments of the invention, and is also not to be construed as limiting the scope of the invention in any way.

Example 1

Methods:

Patients:

Patients with unipolar or bipolar depression admitted as in-patients to the Max Planck Institute of Psychiatry (MPI), Munich, Germany, for treatment of a depressive episode were included in the study. Patients were diagnosed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. Patients with bipolar disorder or depressive disorder due to a general medical or neurological condition were excluded, as were patients with a lifetime diagnosis of drug abuse and depressive symptoms secondary to alcohol or substance abuse or dependency. Ethnicity was recorded using a self-report sheet for

nationality, first language and ethnicity of the patient and of all four grandparents. All patients were Caucasian and part of the Munich-Antidepressant-Response-Signature (MARS) project (Hennings *et al.*, J Psychiatr Res., 2009) (www.mars-depression.de). They were treated with antidepressant medications according to doctor's choice. Severity of depressive symptoms was assessed at admission and at the time of the dex/CRH test by trained raters using the 17-item Hamilton Depression Rating Scale (HAM-D, Hamilton, J Neurol Neurosurg Psychiatry, 1960). 192 patients fulfilling the criteria for at least a moderate to severe depressive episode (HAM-D≥18) at both time points and who had been administered a dex/CRH test within 10 days of in-patients admission and had genome-wide SNP data were included in this analysis. The study was approved by the Ethics Committee of the Ludwig Maximilians University in Munich, Germany, and written informed consent was obtained from all subjects.

Dex/CRH test:

The dex/CRH test was administered as described in detail in Heuser *et al.* (J Psychiatr Res., 1994). In brief, subjects were pre-treated with 1.5 mg of dexamethasone per os at 11 pm. The following day, at 3 pm, 3.30 pm, 3.45 pm, 4 pm and 4.15 pm blood was drawn. An intravenous bolus of 100 µg of human CRH (Ferring, Kiel, Germany) was given at 3.02 pm. Plasma ACTH concentrations were assessed by an immunometric assay without extraction (Nichols Institute, San Juan Capistrano, California; USA). The neuroendocrine response to the dex/CRH test was analyzed using the total area under the curve (AUC) of the ACTH response.

SNP Genotyping:

After enrollment in the study 40 ml of EDTA blood was drawn from each patient. DNA was extracted from fresh blood using the Puregene® whole blood DNA-extraction kit (Gentra Systems Inc; MN). Genotyping was performed on Illumina Human 610k quad genotyping arrays (Illumina Inc., San Diego, USA) according to the manufacturer's standard protocols. The average call rate exceeded 99 %, with samples below 98 % being either retyped or excluded from the study. The reproducibility for samples genotyped twice was 99.99 % or better.

Data analysis:

To identify genetic predictors for the ACTH response to the dex/CRH test in patients with moderate to severe depression, the 192 patients were randomly split into a training (N = 96) and test set (N = 96). The demographic and clinical descriptors of these two samples are given in table 3.

Table 3:

Demographic and clinical description of the 192 patients in the trainings and test set.

	training set	test set	p-value
N	96	96	
% female	52,1	57,2	n.s.
% bipolar (1 or 2)	12,5	12,5	n.s.
% with psychotic symptoms	15,2	11,4	n.s.
age (mean years (SD))	47,2 (14,2)	51,3 (13,2)	0,038
BMI at admission (mean SD)	24,9 (4,1)	24,9 (4,3)	n.s.
age-on (mean years (SD))	34,72 (14,5)	36,6 (15,9)	n.s.
number of previous episodes (mean N (SD))	3,2 (4,0)	3,3 (4,7)	n.s.
depression severity at admission (mean HAMD-17 score (SD))	26,4 (4,4)	27,7 (4,8)	0,058
depression severity at dex-crh test (mean HAMD-17 score (SD))	26,9 (5,0)	28,5 (5,0)	0,029
Cortisol AUC (mean (SD))	3611,4 (3414)	3688,6 (3491)	n.s.
ACTH AUC (mean (SD))	1246 (910)	1482,8 (1319)	n.s.
days after admission when dex-CRH test was performed	6,1 (2,2)	5,9 (2,2)	n.s.

After natural log transformation of the AUC of the ACTH response in the dex/CRH test, patients were dichotomized into high vs. low responders. For the ACTH AUC the cut-off was ln ACTH AUC > 7.0. This placed 46.4% (89 out of a total of 192 individuals) in the high responder class. See the corresponding histogram in Figure 1.

Using an additive genetic model and a logistic regression with sex and age as covariates in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/), the association of all SNPs with a MAF > 0.05 were tested on the 610k arrays with the dichotomized response for cortisol and ACTH in the dex/CRH test in the training set. The top 30 associated SNPs were then used to predict either ACTH or cortisol response status in the test set using a "Probabilistic Neural Network und General Regression Neural Network" approach (implementation DTREG 10.3.3 www.dtreg.com). All values were derived from a 20 fold cross validation.

Results:

The top 30 association with ACTH response status are given in table 4. Association p-values ranged from 5.0 e-5 to 2.3 e-4 for the ACTH response.

The genotypes for the 30 SNPs each were then used to predict ACTH response status in the second, independent test cohort (subgroup of the test set).

Table 4: List of 30 SNPs used to predict ACTH AUC in the second test cohort.

SNP	Chromosome	Coordinate_HG18	P-value training	GeneVariant	GeneName
rs6437726	chr3	108321446	5.037e-005	INTERGENIC	N/A
rs1986684	chr11	110629697	5.287e-005	UPSTREAM	N/A
rs7380830	chr5	66022641	5.459e-005	INTRONIC	ENSG0000019656
rs3903768	chr13	49294756	6.811e-005	INTERGENIC	N/A
rs7325978	chr13	71960761	8.206e-005	INTERGENIC	N/A
rs13585	chr22	45131843	0.0001016	REGULATORY_REGION,3PRIME_UTR	TRMU
rs9368373	chr6	22024631	0.0001063	INTERGENIC	N/A
rs10935354	chr3	141026326	0.0001073	INTERGENIC	N/A
rs8095703	chr18	11041081	0.0001183	INTERGENIC	N/A
rs10206851	chr2	5381477	0.0001267	INTERGENIC	N/A
rs9542977	chr13	71958236	0.0001499	INTERGENIC	N/A
rs4942879	chr13	49314940	0.0001537	INTERGENIC	N/A
rs9542954	chr13	71918308	0.0001643	INTERGENIC	N/A
rs1593478	chr18	2292023	0.0001663	INTERGENIC	N/A
rs9542951	chr13	71913959	0.0001664	INTERGENIC	N/A
rs2188534	chr7	111837550	0.0001823	INTERGENIC	N/A
rs12524124	chr6	22051921	0.000185	INTERGENIC	N/A
rs4352629	chr5	87792577	0.0001985	INTERGENIC	N/A
rs7448716	chr5	87788451	0.0001985	INTERGENIC	N/A
rs11873533	chr18	3732713	0.0002107	INTRONIC	DLGAP1
rs10062658	chr5	102881920	0.0002216	INTERGENIC	N/A
rs12547917	chr8	142306580	0.0002282	INTRONIC	SLC45A4
rs1038268	chr9	31967623	0.000229	INTERGENIC	N/A
rs2375811	chr9	31979998	0.000229	INTERGENIC	N/A
rs1352671	chr9	32033985	0.000229	INTERGENIC	N/A
rs364331	chr9	32039631	0.000229	INTERGENIC	N/A
rs1924949	chr13	71975473	0.0002323	INTERGENIC	N/A
rs11025990	chr11	21218608	0.0002323	INTRONIC	NELL1
rs3758562	chr10	72032086	0.0002369	INTRONIC	PRF1
rs10156056	chr7	22720613	0.0002394	INTERGENIC	N/A

The results of the prediction in the test set are summarized below:

For the prediction of the dichotomized ACTH response status in the dex/CRH the following prediction values were achieved:

ACTH:

Accuracy = 85.33%

Sensitivity = 87.18%

Specificity = 83.33%

Geometric mean of sensitivity and specificity = 85.23%

Positive Predictive Value (PPV) = 85.00%

Negative Predictive Value (NPV) = 85.71%

Geometric mean of PPV and NPV = 85.36%

Precision = 85.00%

Recall = 87.18%

F-Measure = 0.8608

Area under ROC curve (AUC) = 0.851852

Using genome-wide SNP association data for the ACTH response in the dex/CRH test, a subset of 30 SNPs could be identified that allowed an accurate, sensitive and specific prediction of these phenotypes in independent sets of patients. Increased ACTH secretion in this test has been linked to an increase in central CRH/CRHR1 function. Although environmental, pharmacological and disease state-dependent factors have previously been described to influence the endocrine response to this test in depressed patients (Ising *et al.*, Neuropsychopharmacol Biol Psychiatry, 2005; Heim *et al.* Biol Psychiatry, 2008; Kunzel *et al.* Neuropsychopharmacology, 2003), it has now been shown that genetic polymorphisms alone are strong predictors.

Patients with depression or anxiety disorders, classified into the high ACTH response group according to the genotypes of the presented 30 SNPs described in this example will be more likely to respond to CRHR1 antagonist treatment. This allows an

enrichment of such patients for CRHR1 antagonist treatment studies who will most likely respond to this specific treatment.

Example 2:

Sleep disturbances, such as decreased slow-wave sleep, increased sleep fragmentation and rapid-eye-movement sleep (REMS) disinhibition, are cardinal symptoms of major depression in humans. This study aims to identify those patients where a central CRH hyperdrive plays a causal role and which would therefore respond favourably to a CRHR1 antagonist. To test the relationship between a central CRH-overexpression and REM-disinhibition in particular, transgenic mouse models where CRH is overexpressed as a result of genetic engineering were employed.

Many animal models of depression share increases in REM-sleeps (REMS) as a common feature. Therefore, increased REMS in animals should reflect REMS-disinhibitions in humans. Mice with CNS-specific CRH-overexpression strikingly share the characteristic increases in REMS. As such, an increase in REMS indicates a central hypersecretion of CRH and may serve as a biomarker to identify those patients who would benefit from treatment with a CRHR1 antagonist.

Experiments were conducted with two different mouse lines of excessive central CRH secretion and their respective control littermates (CL). Mice of the CRH-COE^{CNS} line are characterised by CRH-overexpression within the whole CNS, whereas mice of the Cor26 CRH line display a CRH-overexpression specific to CRH-ergic neurons of the CNS. Three different CRHR1 antagonists were tested. While DMP-696 (bicyclic) and CP-316,311 (monocyclic) are class I CRH-R1 antagonists, SSR125543A (long off-rate, typical slow-tight binding inhibitor) belongs to class II CRH-R1 antagonists. DMP-696 and SSR125543A were applied to CRH-COE^{CNS} mice (n_{DMP696}= 6/6 COE/CL; $n_{SSR125543}$= 6/5 COE/CL), while CP-316,311 was tested in Cor26 CRH mice ($n_{CP316.311}$= 5/3 Cor26/CL). In all cases, animals were left to recover from EEG/EMG-electrode implantation for two weeks, after which two days of baseline recording were initiated. Treatment with CRH-R1

antagonist or respective vehicle control commenced thereafter for five consecutive days. Antagonists were applied through the drinking water at a daily dose of 50mg/kg body weight. EEG and EMG recordings were manually scored as wake, non-REMS (NREMS), and REMS in four second epochs by an experienced evaluator.

As previously shown, CRH-COE^{CNS} mice display significantly higher REMS activity under baseline condition as compared to controls. Chronic DMP-696 (50mg/kg/d DMP-696) treatment entails only a mild suppression of REMS in CL mice. However, DMP-696-treated CRH-COE^{CNS} mice show a significant decrease in REMS activity beginning with treatment day two ($P<0.05$). The strongest suppression of REMS activity in CRH-COE^{CNS} animals could be observed on treatment day three (Figure 2).

Comparable to DMP696 treatment, oral application of SSR125543A (50mg/kg/d) affected REMS levels in CRH-overexpressing mice. No effects of SSR125543 on REMS activity in control animals could be detected. In contrast, a significant suppression of REMS could be observed beginning with day two in CRH-overexpressing animals ($P\leq0.035$). Similar to DMP696 treatment, REMS suppression in CRH-COE^{CNS} mice never exceeded baseline REMS-levels of CL (Figure 3).

Application of CP-316,311 (Pfizer) in the Cor26 CRH mouse line showed no significant effect on REMS levels in CL animals (data not shown). Similarly, in CRH-overexpressing Cor26 CRH mice suppression in REMS apparently seemed weak. However, comparison of the area under the curve (AUC) within the light period of baseline and treatment day three showed a significant decrease ($P=0.006$) of REMS levels after CP-316,311 application (Figure 4).

CRH is one of the major drivers of the stress response in the brain. Hyperactivity of the CRH system seems to be responsible for cognitive impairments, emotional responses, and behavioural changes which are typical for depression. One of those

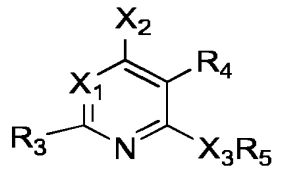
behavioural changes are sleep disturbances exemplified by REMS disinhibition. The link between CRH-overexpression and REMS level increases is evidenced by the mouse lines used in these experiments. Since CRH-overexpression in the Cor26 CRH mouse line is limited to CRH-ergic neurons, the net increase of CRH is lower when compared to the whole brain overexpression in CRH-COE^{CNS} mice. As a result, the phenotype of increased REMS levels was less profound in Cor26 CRH mice as compared to CRH-COE^{CNS} animals.

The main finding of this study is that the normalization of CRH-elicited sleep-EEG disturbances is striking when (1) different chemical classes of CRHR1 antagonists are used and (2) different animal models for CRH-induced sleep-EEG changes that are typical for human depression are employed. REMS disinhibition is indicative of a central CRH dysfuntion (i.e. hyperactivity) and as such may serve as a biomarker for the identification of depressed patients where depression is caused by central CRH-hyperdrive. Normalization of the sleep pattern by application of different CRHR1 antagonists could be shown in all of our experiments, employing different classes of CRHR1 receptors and different animal models overexpressing centrally CRH.

Claims

1. Corticotropin releasing hormone receptor type 1 (CRHR1) antagonist for use in the treatment of depressive symptoms and/or anxiety symptoms in patients having corticotropin releasing hormone (CRH) overactivity.

2. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein

X_1 is $-CR_6$ or N;

X_2 is $-NR_1R_2$, $-CR_1R_2R_9$, $-C(=CR_2R_{10})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{10}$, $-CHR_2SR_{10}$, $-C(S)R_2$ or $-C(O)R_2$;

X_3 is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{11}R_{12})$, wherein R_{11} and R_{12} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{11} and R_{12} is cyano and the other is hydrogen or methyl, or

X_3 is N and X_3 and R_4 form a 5-membered ring substituted at X_3 with R_5;

R_1 is $C_1\text{-}C_6$ alkyl which may optionally be substituted with one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_4$ alkoxy, $-O\text{-}CO\text{-}(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}NH(C_1\text{-}C_4$ alkyl), $-O\text{-}CO\text{-}N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $-NH(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_2$ alkyl)$(C_1\text{-}C_4$ alkyl), $-S(C_1\text{-}C_4$ alkyl), $-N(C_1\text{-}C_4$ alkyl)$CO(C_1\text{-}C_4$ alkyl), $-NHCO(C_1\text{-}C_4$ alkyl), $-COO(C_1\text{-}C_4$ alkyl), $-CONH(C_1\text{-}C_4$ alkyl), $-CON(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), CN, NO_2, $-SO(C_1\text{-}C_4$ alkyl) and $-SO_2(C_1\text{-}C_4$ alkyl), and

wherein said C_1-C_6 alkyl and the (C_1-C_4) alkyl moieties in the foregoing R_7 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, C_1-C_{12} alkoxyalkyl,
aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, oxadiazolyl or benzoxazolyl;

3- to 8-membered cycloalkyl or –(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_8 wherein R_8 is hydrogen or C_1-C_4 alkyl;

and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and/or the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or –$CR_1R_2R_9$ may form a saturated 5- to 8-membered ring which may optionally contain one or two carbon-carbon double bonds and/or in which one or two of the ring carbons may optionally be replaced by an oxygen, nitrogen or sulfur atom and which may be substituted with at least one substituent;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy,
-CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OCF3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$ -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4

alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and/or may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -$NH(C_1$-C_2 alkyl), -$N(C_1$-C_2 alkyl)$_2$, -$COO(C_1$-C_4 alkyl), -$CO(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl,

wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, (C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -$COO(C_1$-C_4 alkyl), -$CO(C_1$-C_4 alkyl), -$SO_2NH(C_1$-C_4 alkyl), -$SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2(C_1$-C_4 alkyl), -$S(C_1$-C_6 alkyl) and $SO_2(C_1$-C_6 alkyl), and wherein the C_1-C_4 alkyl and the C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -$O(C_1$-C_4 alkyl), -$C(O)(C_1$-C_4 alkyl), -$C(O)O(C_1$-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_9 is hydrogen, hydroxy, fluoro, or methoxy;

R_{10} is hydrogen or C_1-C_4 alkyl.

3. CRHR1 antagonist for use according to claim 2, wherein
X_1 is $-CR_6$.

4. CRHR1 antagonist for use according to claim 3, wherein X_1 is CH.

5. CRHR1 antagonist for use according to any of claims 2 to 4, wherein the 5- to 8-membered ring formed by $-NR_1R_2$ or $-CR_1R_2R_9$ is substituted with at least one substituent selected from C_1-C_4 alkyl or
with a 4-8 membered ring, which may be saturated or may contain one to three double bonds and in which one carbon atom may be replaced by CO or SO_2 and one to four carbon atoms may optionally be replaced by nitrogen.

6. CRHR1 antagonist for use according to any of claims 2 to 4, wherein
X_2 is $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-NR_1R_2$.

7. CRHR1 antagonist for use according to claim 6, wherein
$-NHCHR_1R_2$ is $-NHCH(CH_2OCH_3)_2$, $-NHCH(CH_2OCH_3)(CH_2CH_3)$, $-NHCH(CH_2CH_3)_2$, $-NHCH(CH_2CH_2OCH_3)_2$, $-NHCH(CH_3)(CH_2CH_3)$ or $-NHCHR_1R_2$, wherein R_1 is ethyl and R_2 is oxadiazolyl substituted with methyl, isopropyl, cyclopropyl, trifluoromethyl, or ethyl,
or
$-NR_1R_2$ is $-N(CH_2CH_3)(CH_3)$, $-N(CH_2CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)$(cyclopropyl), $-N(CH_2CH_3)(CH_2CH_2CH_2CH_3)$, $-N(CH_2CH_2OCH_3)_2$, or $-N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$
or
$-OCHR_1R_2$ is $-OCH(CH_2CH_3)_2$, $-OCH(CH_2CH_3)CH_3$, $-OCH(CH_2CH_3)(CH_2CH_2CH_3)$, $-OCH(CH_2CH_3)(CH_2OCH_3)$.

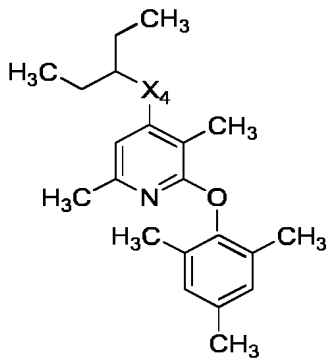
8. CRHR1 antagonist for use according to any of claims 2 to 7, wherein
R_3 and R_4 are methyl.

9. CRHR1 antagonist for use according to any of claims 2 to 8, wherein

X_3 is O.

10. CRHR1 antagonist for use according to any of claims 2 to 9, wherein
R_5 is phenyl substituted with from one to three substituent(s) independently selected from the group CH_3, CH_2CH_3, OCH_3, Cl, F, CF_3.

11. CRHR1 antagonist for use according to any of claims 1 to 10, wherein the CRHR1 antagonist is a compound of the formula (VI)



(VI)

or a pharmaceutically acceptable salt thereof, wherein
X_4 is O or NH.

12. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class I CRHR1 antagonist.

13. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is a class II CRHR1 antagonist.

14. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is selected from the group consisting of CP154,526, Antalarmin, CRA 5626, Emicerfont, DMP-696, DMP-904, DMP-695, SC-241, BMS-561388, Pexacerfont, R121919, NBI30545, PD-171729, Verucerfont, NBI34041, NBI35965,

SN003, CRA0450, SSR125543A, CP-316,311, CP-376,395, NBI-27914, ONO-2333Ms, NBI-34101, PF-572778, GSK561579 and GSK586529.

15. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is DMP-696.

16. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is CP-316,311.

17. CRHR1 antagonist for use according to claim 1, wherein the CRHR1 antagonist is SSR125543A.

18. CRHR1 antagonist for use according to any of the preceding claims, wherein CRH overactivity is detected by determining the status of one or more markers indicative for CRH overactivity.

19. CRHR1 antagonist for use according to claim 18, wherein the marker is selected from the group consisting of a biomarker, a set of biomarkers and a clinical marker.

20. CRHR1 antagonist for use according to any of claim 19, wherein the biomarker or the set of biomarkers is obtained by a genome-wide screening for single nucleotide polymorphisms in patients with depressive and/or anxiety symptoms.

21. CRHR1 antagonist for use according to claims 19 or 20, wherein the biomarker or the set of biomarkers is selected from the group comprising:

- SNP rs6437726,
- SNP rs1986684,
- SNP rs7380830,
- SNP rs3903768,
- SNP rs7325978,

- SNP rs13585,
- SNP rs9368373,
- SNP rs10935354,
- SNP rs8095703,
- SNP rs10206851,
- SNP rs9542977,
- SNP rs4942879,
- SNP rs9542954,
- SNP rs1593478,
- SNP rs9542951,
- SNP rs2188534,
- SNP rs12524124,
- SNP rs4352629,
- SNP rs7448716,
- SNP rs11873533,
- SNP rs10062658,
- SNP rs12547917,
- SNP rs1038268,
- SNP rs2375811,
- SNP rs1352671,
- SNP rs364331,
- SNP rs1924949,
- SNP rs11025990,
- SNP rs3758562, and/or
- SNP rs10156056.

22. CRHR1 antagonist for use according to any of claims 19 to 21, wherein the biomarker or the set of biomarkers constituting a marker for CRH activity is selected from one or more biomarkers from the group comprising:

- SNP rs6437726 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 1, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1986684 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 2, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7380830 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 3, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs3903768 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 4, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs7325978 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 5, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs13585 which is represented by a single polymorphic change at position 185 of SEQ ID NO: 6, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9368373 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 7, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs10935354 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 8, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs8095703 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 9, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs10206851 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 10, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,

- SNP rs9542977 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 11, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs4942879 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 12, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs9542954 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 13, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1593478 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 14, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs9542951 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 15, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs2188534 which is represented by a single polymorphic change at position 200 of SEQ ID NO: 16, wherein in one or two alleles the wild-type nucleotide G is replaced by indicator nucleotide T,
- SNP rs12524124 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 17, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs4352629 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 18, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs7448716 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 19, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11873533 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 20, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,

- SNP rs10062658 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 21, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs12547917 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 22, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs1038268 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 23, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide T,
- SNP rs2375811 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 24, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs1352671 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 25, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs364331 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 26, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide C,
- SNP rs1924949 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 27, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs11025990 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 28, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G,
- SNP rs3758562 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 29, wherein in one or two alleles the wild-type nucleotide A is replaced by indicator nucleotide G, and/or
- SNP rs10156056 which is represented by a single polymorphic change at position 201 of SEQ ID NO: 30, wherein in one or two alleles the wild-type nucleotide C is replaced by indicator nucleotide G.

23. CRHR1 antagonist for use according to any of claims 19 to 22, wherein the set of biomarkers comprises at least 15, at least 20 or at least 25 of the biomarkers as defined in claims 21 or 22.

24. CRHR1 antagonist for use according to any of claims 19 to 23, wherein the set of biomarkers consists of the biomarkers as defined in claims 21 or 22.

25. CRHR1 antagonist for use according to any of claims 18 or 24, wherein the biomarker is REM density.

26. CRHR1 antagonist for use according to any of claims 18 or 25, wherein the marker is a combination of a biomarker or set of biomarkers as defined in any of claims 20 to 24 with the biomarker REM density.

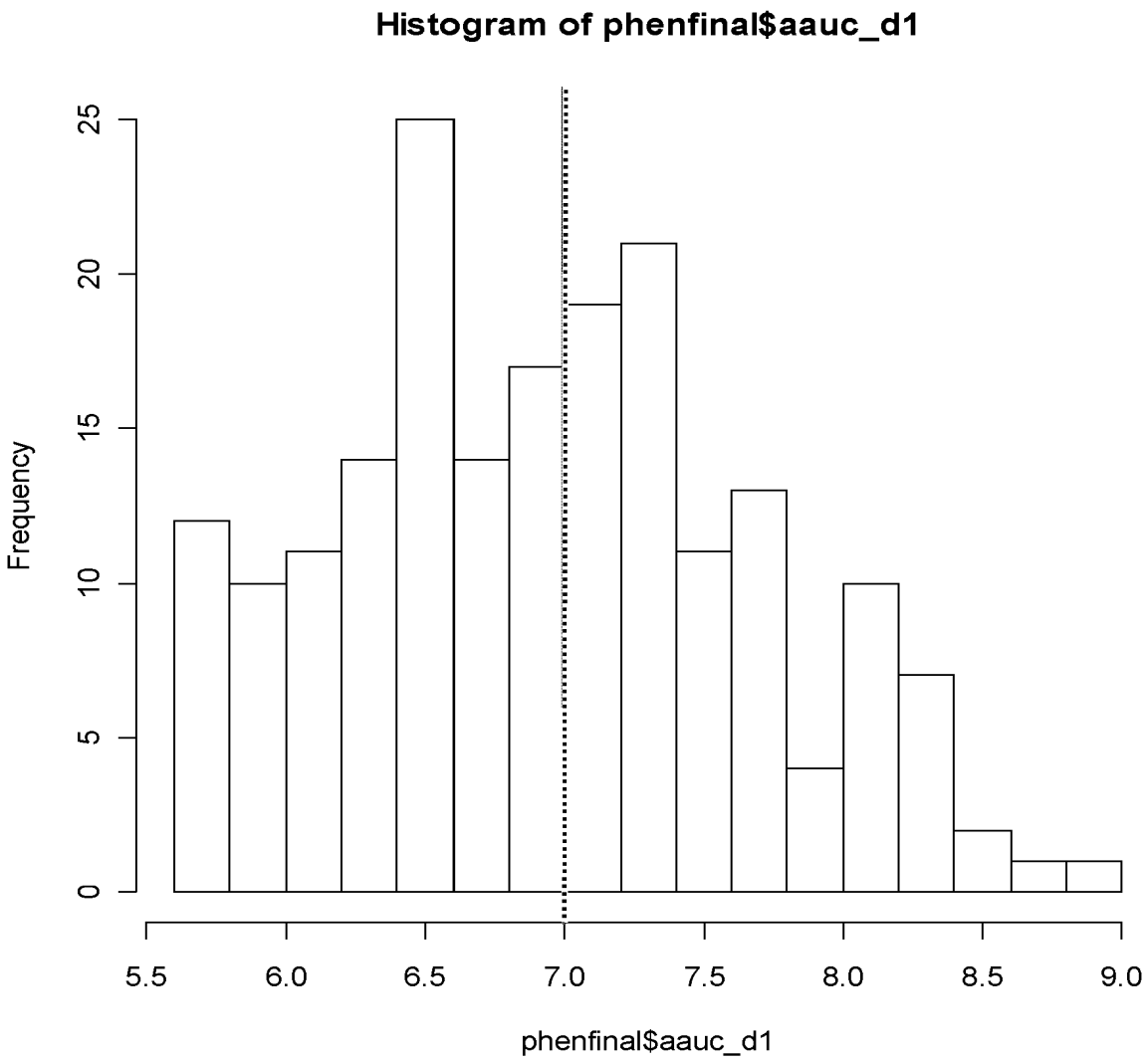

Histogram of phenfinal$aauc_d1
Frequency
0
5
10
15
20
25
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
phenfinal$aauc_d1

Fig. 1

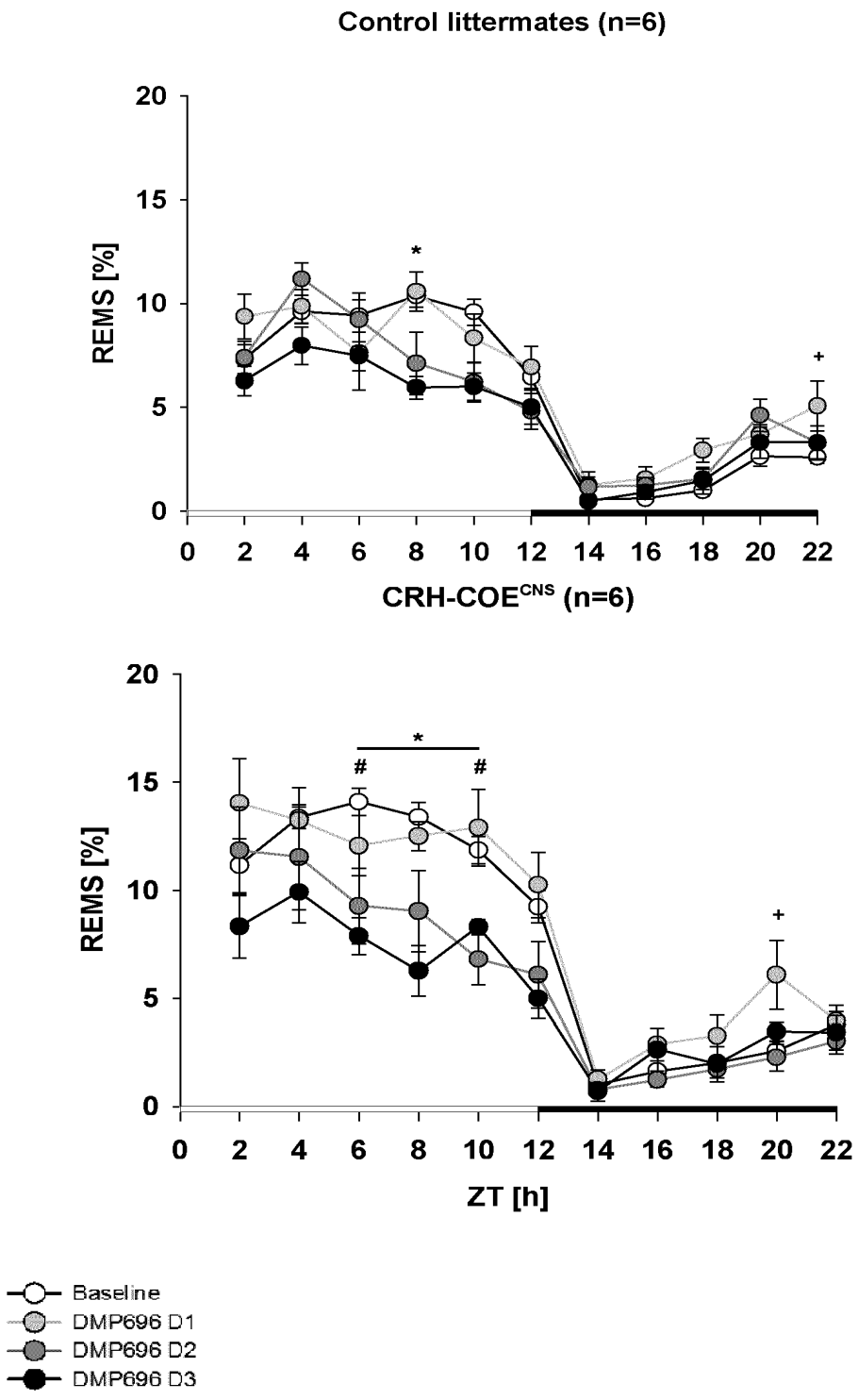

Control littermates (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
+
CRH-COE^{CNS} (n=6)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22
*
#
#
+
ZT [h]
Baseline
DMP696 D1
DMP696 D2
DMP696 D3

Fig. 2

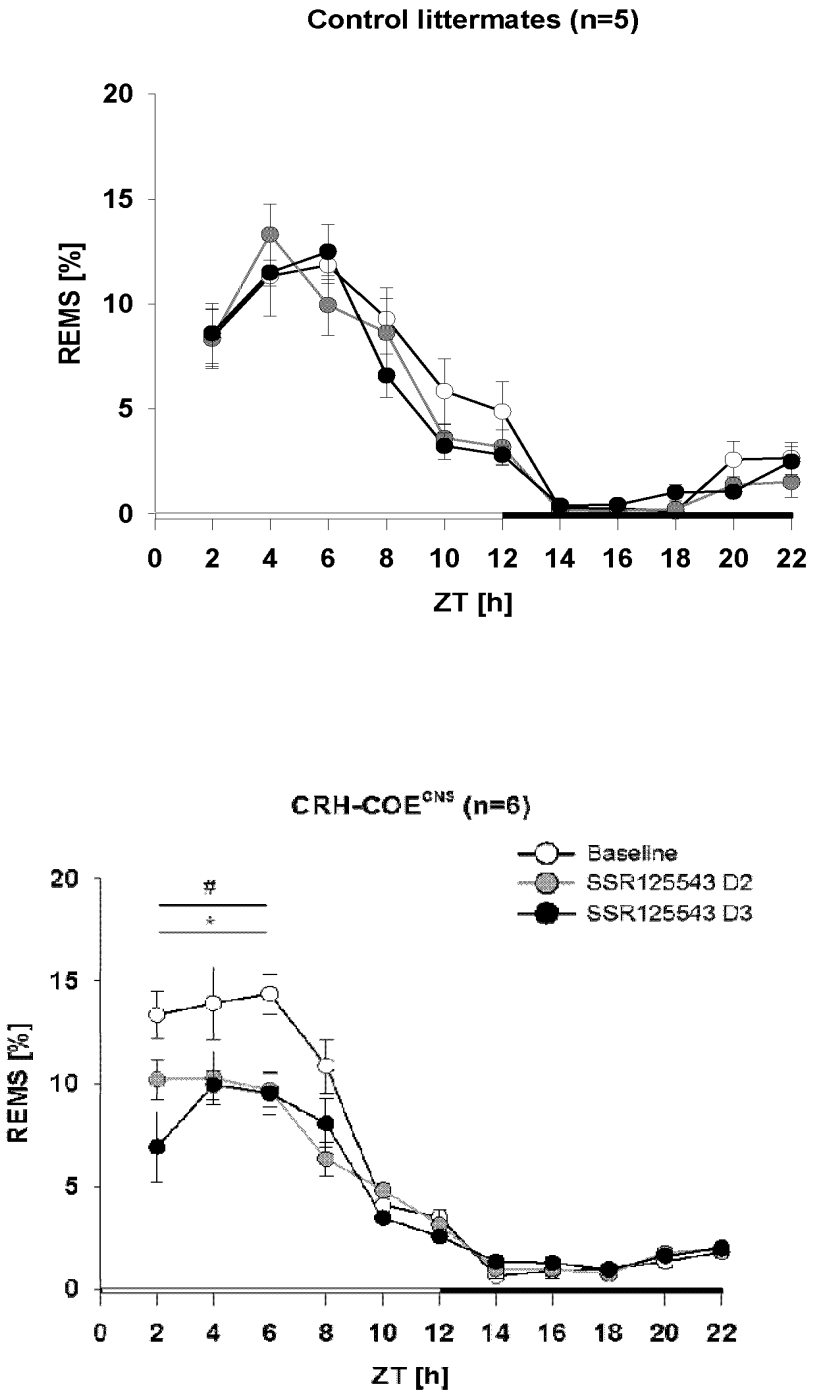

Control littermates (n=5)
REMS [%]
ZT [h]
CRH-COE^CNS (n=6)
Baseline
SSR125543 D2
SSR125543 D3
#
*

Fig. 3

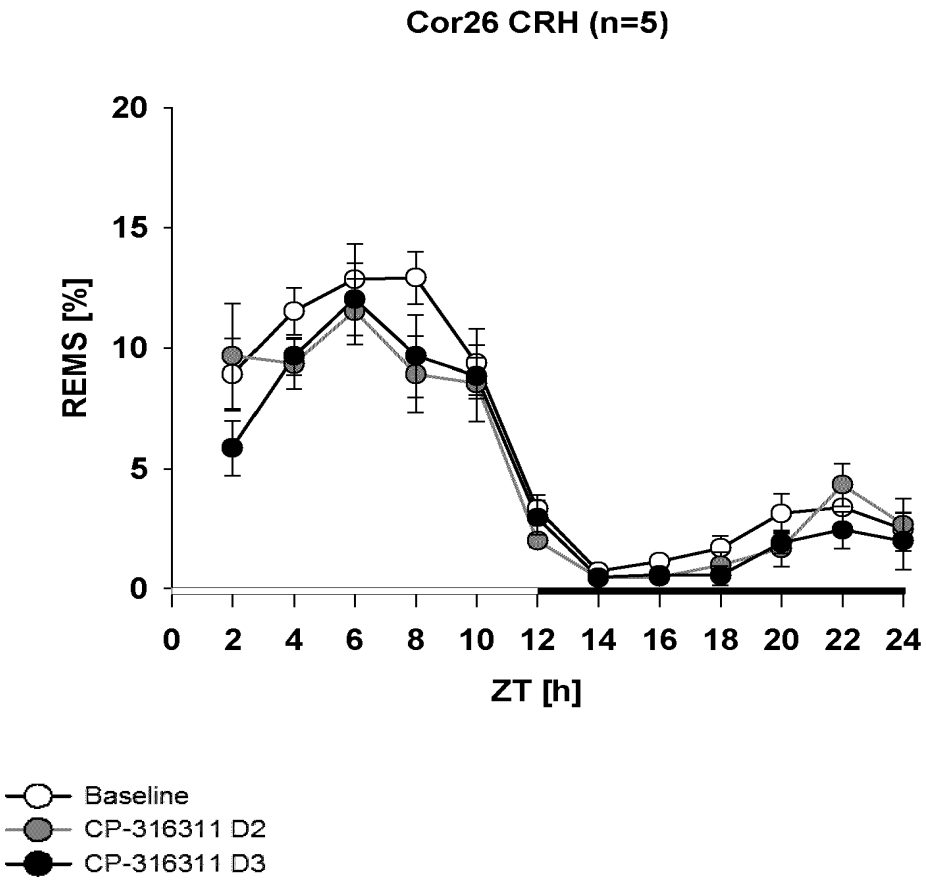

Cor26 CRH (n=5)
REMS [%]
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24
ZT [h]
Baseline
CP-316311 D2
CP-316311 D3

Fig. 4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 April 2010 (08.04.2010)

PCT

(10) International Publication Number
WO 2010/039678 A1

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/US2009/058722

(22) International Filing Date:
29 September 2009 (29.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/102,153 2 October 2008 (02.10.2008) US

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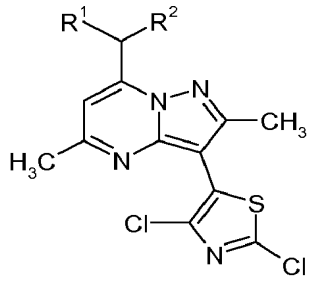
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

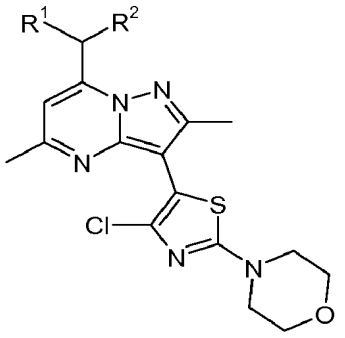
[Continued on next page]

(54) Title: THIAZOLYL-PYRAZOLOPYRIMIDINE COMPOUNDS AS SYNTHETIC INTERMEDIATES AND RELATED SYNTHETIC PROCESSES

(57) Abstract: The present invention relates to a synthetic intermediate of the formula (I) and its use in a synthetic process to make compounds of the formula (II).



(I)



(II)

WO 2010/039678 A1

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

THIAZOLYL-PYRAZOLOPYRIMIDINE COMPOUNDS AS SYNTHETIC INTERMEDIATES AND RELATED SYNTHETIC PROCESSES

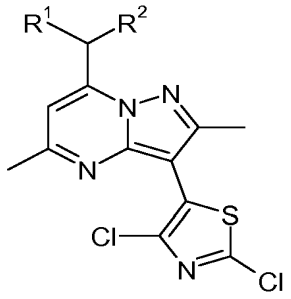
This invention relates to novel intermediates and processes in the synthesis of thiazolyl-pyrazolopyrimidine compounds, which final compounds are useful as CRF-1 receptor antagonists for the treatment of certain psychiatric and neuroendocrine disorders.

Corticotropin releasing factor (CRF) is a peptide hypothalamic hormone which also has a broad spectrum of physiological effects consistent with a neurotransmitter or neuromodulator role in the brain. CRF has been implicated in a wide range of psychiatric disorders and neurological diseases including alcohol and substance abuse and associated withdrawal symptoms, as well as depression and anxiety. CRF-1 receptor antagonists have particularly been implicated for the treatment of alcohol dependency and depression.

Certain thiazolyl-pyrazolo[1,5-*a*]pyrimidines have been found to be particularly useful as CRF-1 antagonists, as for example 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine and 7-(1-propyl-butyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, as described in WO 2008/036579. Recent advances in copper catalyzed arylation reactions with different substrates have been described in J. Am. Chem. Soc., vol. 130, pg. 1128-1129 (2008).

The present invention provides novel synthetic intermediates and synthetic processes using said intermediates to make thiazolyl-pyrazolo[1,5-*a*]pyrimidine CRF-1 receptor antagonists more economically and in higher yields. Certain embodiments of the presently claimed processes also avoid the use of mutagenic materials and environmentally toxic catalysts, as compared to previously known synthetic methods, as for example, those disclosed in WO 2008/036579.

In one aspect of the present invention, there is provided a compound of Formula I



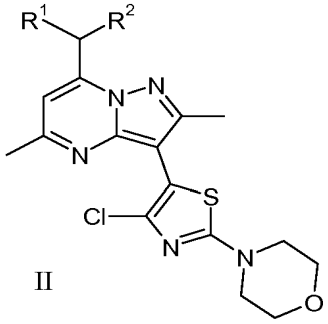
Formula I

wherein:

R^1 and R^2 are independently ethyl or *n*-propyl.

In one preferred embodiment, R^1 and R^2 are each ethyl. In a second preferred embodiment, R^1 and R^2 are each *n*-propyl.

In another aspect of the present invention, there is provided a synthetic process for preparing a compound of the Formula II

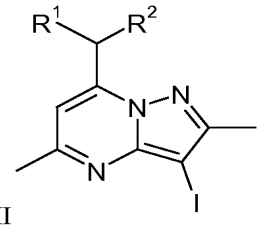


II

wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

i) reacting a compound of Formula III,



III

or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine,

and a base selected from K_3PO_4 and Cs_2CO_3, to form a compound of Formula I (above); and

ii) reacting the compound of Formula I, with morpholine, or a salt thereof, in the presence of a suitable inorganic base.

In one preferred embodiment of this aspect of the invention, R^1 and R^2 are each ethyl. In a second preferred embodiment of this aspect of the invention, R^1 and R^2 are each *n*-propyl.

Suitable copper halide catalysts include CuI, CuBr, and CuCl. CuCl is preferred.

Use of a copper ligand facilitates the efficient catalysis by the copper ion. Both 1,10-phenanthroline and bipyridine are effective ligands in the present process. 1,10-phenanthroline is preferred. When bipyridine is used, higher mole percents of bipyridine and copper are needed for high yields, as for example from about 0.9 to about 1.1 equivalents, say about 1 equivalent bipyridine, and from about 0.5 to about 1.1 equivalents of the copper source, say about 1 equivalent of the copper source, with CuCl being preferred.

When 1,10-phenanthroline is used, it may be effectively used in catalytic amounts, and with catalytic amounts of the copper source, as for example from about 5-50 mole percent each (0.05-0.50 equivalents), with CuCl being the preferred copper source. In one embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl , are used at about 5-50 mole percent (0.05-0.50 equivalents). In another embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl, are used at about 10 ± 1 mole percent (0.10 equivalents). In yet another embodiment, the 1,10-phenanthroline and the copper catalyst, say CuCl, are used at about 30 ± 1 mole percent (0.30 equivalents).

The reaction of step i) is base driven and is sensitive to the base selected. The dichlorothiazole reagent is base and temperature labile and is susceptible to degradation if the selected base is too strong and/or the reaction temperature is too high, as for example with *t*-butoxy lithium or *t*-butoxy potassium and/or at temperatures higher than about 120° C. As such, suitable bases for step i) are K_3PO_4 and Cs_2CO_3, with Cs_2CO_3- being preferred. Likewise, it is preferred that the reaction of step i) be run at a temperature of from about 80 to 120° C.

The reaction of step i) is less sensitive to the solvent selected with suitable solvents being aprotic solvents, as for example 1,4-dioxane, 2-MeTHF, DMAC, CPME, propanenitrile, 2-MeTHF/DMAC, *n*-BuOAc and DMF. The co-solvent system of 2-MeTHF/DMAC with proportions in the range of 70/30 to 80/20 being preferred, as for example 80/20 2-MeTHF/DMAC.

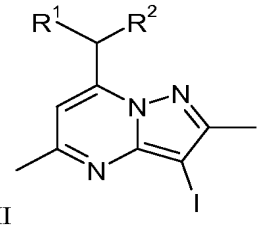
The reaction of step ii) is less sensitive to the inorganic base and solvent selected. Suitable bases include K_2CO_3, Cs_2CO_3, Na_2CO_3, K_3PO_4, NaOH, and the like. K_2CO_3 and K_3PO_4 are preferred with K_2CO_3 being particularly preferred.

Suitable solvents for the reaction of step ii) include most polar solvents, such as methanol, ethanol, n-propanol, 2-propanol, n-butanol, acetonitrile, 2-MeTHF, and morpholine. Morpholine is preferred in that it is an excellent solvent and a reactant in the reaction of step ii).

Preferred reaction temperatures for the reaction of step ii) are from about 60 - 120° C.

In one preferred embodiment of the present invention, the synthetic process comprises the steps of:

i) reacting a compound of Formula III,



III

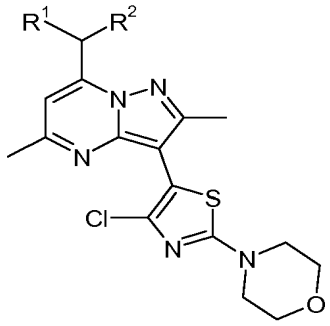
or a salt thereof, wherein R^1 and R^2 are independently ethyl or *n*-propyl, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of CuCl, 1,10-phenanthroline, and a base selected from K_3PO_4 and Cs_2CO_3, to form a compound of Formula I (above); and

ii) reacting the compound of Formula I, with morpholine, or a salt thereof, in the presence of K_2CO_3.

It is further preferred in this embodiment of the process that the reaction of step i) use from about 5-50 mole percent, particularly about 30 mole percent, CuCl and from about 5-50 mole percent, particularly about 30 mole percent, 1,10-phenanthroline with 2-MeTHF/DMAC (particularly about 80/20 2-MeTHF/DMAC) as a solvent system and

that the reaction be run at from about 80 to 120° C, and that the reaction of step ii) use morpholine as a solvent and K_2CO_3 as the base.

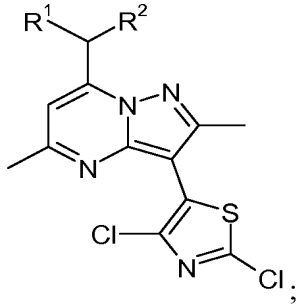
In a another aspect of the invention, there is provided a synthetic process for preparing a compound of the formula



wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

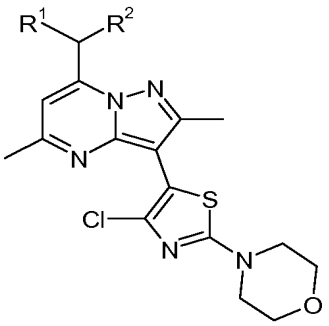
i) reacting a compound of the formula



;

or a salt thereof, with an excess of morpholine or salt thereof, in the presence of a suitable solvent.

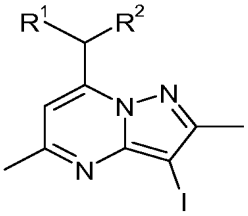
One embodiment of this aspect of the invention provides a synthetic process for preparing a compound of the formula



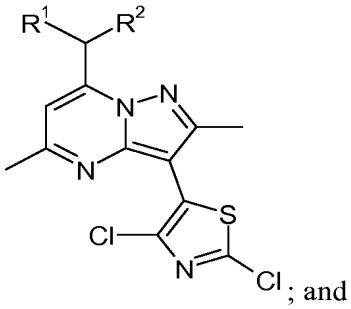
wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3, to form a compound of the formula



; and

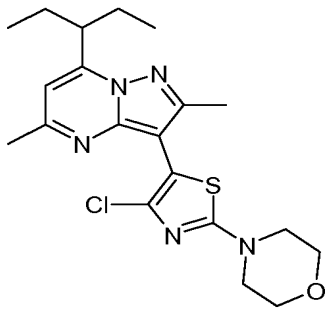
ii) reacting the product of step i), with an excess of morpholine, or a salt thereof, in a suitable solvent.

In this aspect of the invention, various aprotic solvents may be suitable, but preferred solvents are 2-MeTHF and 2-propanol. In a preferred embodiment, 2-propanol is used as solvent. It is surprisingly found that use of 2-propanol reduces reaction times about three fold over prior solvent systems tested. It is also surprisingly found that use of

2-propanol provides the desired amination product in high purity even in the presence of competing nucleophilic alcohol. Use of 2-propanol also further simplifies the work up of the final product by allowing crystallization directly from this solvent, thus avoiding a further solvent exchange prior to crystallization.

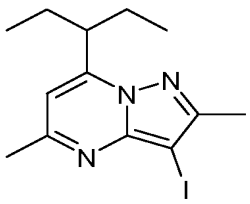
In this aspect of the invention, it has also been surprisingly found that morpholine can function as a suitable base for the amination reaction, thus eliminating the need for an additional base to drive the reaction. Additionally, yields are improved while maintaining quality of final product. Reduction of the amount of morpholine used is also of benefit in the final workup of the product. In one embodiment wherein 2-MeTHF is used as the solvent, the reaction is run with between about 4.0 and about 6.0 equivalents, say about 5.35 equivalents, of morpholine, or salt thereof. In another embodiment wherein 2-propanol is used as the solvent, the reaction is run with between about 3.0 and about 4.0 equivalents, say about 3.3 equivalents, of morpholine, or salt thereof.

Thus in one embodiment of the invention, there is provided a synthetic process for preparing a compound of the formula

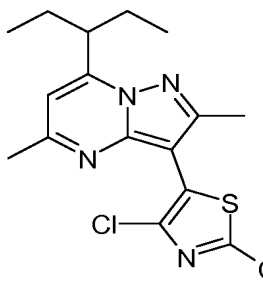


comprising the steps of

i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of copper chloride, 1,10-phenanthroline, and Cs_2CO_3, to form a compound of the formula



; and

ii) reacting the product of step i), with an excess of morpholine, or a salt thereof, in 2-propanol as a solvent.

Abbreviations use in this application are as follows:

CPME means cyclopentyl methyl ether.

DMAC means N,N-dimethylacetamide.

DMF means dimethylformamide.

EtOAc means ethylacetate.

2-MeTHF means 2-methyltetrahydrofuran.

2-MeTHF/DMAC system means 2-methyltetrahydrofuran and N,N-dimethylacetamide in a co-solvent system in proportions between about 70/30 and about 80/20.

n-BuOAc means n-butylacetate.

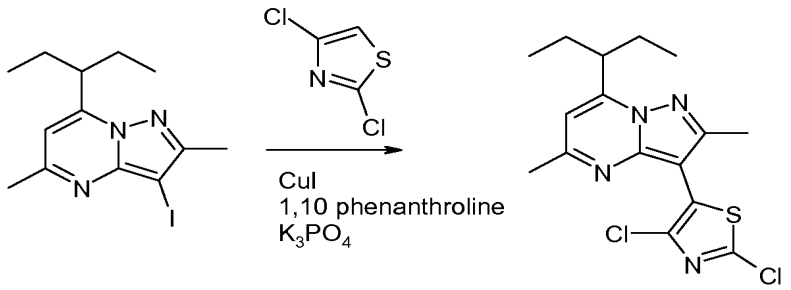
XRPD means X-ray powder diffraction.

DSC means differential scanning calorimetry.

Further preferred embodiments for the synthetic process of the present invention are as described in the examples below.

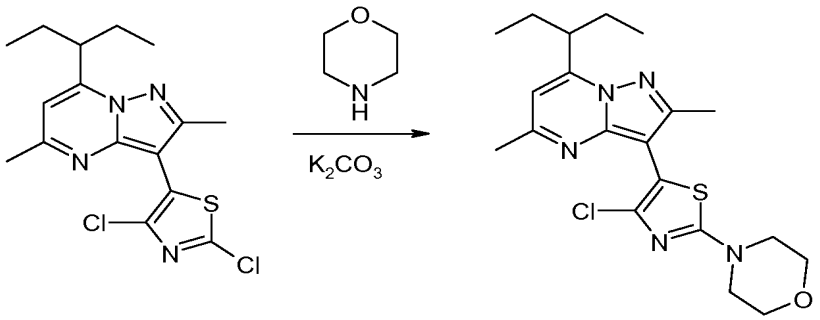
EXAMPLES

Example 1: 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine



Charge 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (1.03 g, 3.00 mmoles), K_3PO_4 (1.95 g, 9.00 mmoles), 2,4-dichlorothiazole (0.58 g, 3.75 mmoles), 1,10 phenanthroline (0.05 g, 0.30 mmoles) and anhydrous DMAC (5 mL) to a round bottom flask equipped with a magnetic stir bar, thermal couple and N_2 inlet. Degas the yellow heterogeneous reaction mixture with N_2 (gas) for 30 min. and then add CuI (0.06 g, 0.30 mmoles) in one portion followed by additional 30 min. degassing with N_2 (gas). Stir the reaction mixture at 120 °C for about 6 hr. Cool the reaction mixture to room temperature overnight, add toluene (10 mL) and stir for 1 hr. Purify the mixture through silica gel eluting with toluene (10ml). Extract with 1 M HCl (10 mL), water (10 mL), brine (10 mL) and concentrate under reduced pressure to give a yellow solid. Recrystallize the solid from methanol (5ml) to yield the title compound as a yellow crystalline solid. (0.78 g, 70% yield, >99% pure by LC) MS(ES) = 369 (M+1). ^{1}H NMR ($CDCl_3$)= 6.5 (1H, s); 3.6 (1H, m); 2.6 (3H, s); 2.5 (3H, s); 1.9 (4H, m); 0.9 (6H, t).

Example 2: 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine



Charge 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (0.37 g, 1.00 mmoles), K_2CO_3 (0.28 g, 2.00 mmoles) and anhydrous morpholine (3 mL) to a round bottom flask equipped with a magnetic stir bar

and N_2 inlet. Stir the yellow mixture at 100 °C for about 4 hr., during which time the reaction becomes homogeneous. Cool the reaction mixture to room temperature, add H_2O (10 mL) and stir the heterogeneous reaction mixture overnight at room temperature. Collected the yellow solid by filtration, wash with H_2O and allowed to air dry overnight to give the crude title compound (391mg). Recrystallize from isopropyl alcohol (3 mL) to yield the title compound as a light yellow crystalline solid (380 mg, 90.6% yield, >99% by LC). MS(ES) = 420 (M+1). ^{1}H NMR ($CDCl_3$)= 6.45 (1H, s); 3.81 (m, 4H); 3.62 (1H, m); 3.50 (m, 4H); 2.6 (3H, s); 2.45 (3H, s); 1.85 (4H, m); 0.9 (6H, t).

Example 3:

The reactions of Example 1 are run with various other catalysts, ligands, bases and solvents, which are found to have the following effects on yield of 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. (See Tables 1 - 4).

Table 1: Evaluation of different ligands

Ligand	% Product
2,2'-bipyridine	72.7
1,10-phenanthroline	84.7
L-proline	23.7
2-acetylcyclohexanone	19.0

(Reactions are carried out in parallel reactors with 1.2 mmol 2,4-dichlorothiazole, 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.5 mmol CuI, 0.5 mmol ligand and 2.1 mmol Cs_2CO_3 in 4 mL DMAC. The reactions are degassed under N_2 for 30 min. and then heated at between 80 and 100ºC overnight under N_2. Percent product is measured as the percent of total area under the HPLC curve for the product peak. Longer reaction times are shown in parenthesis)

Table 2: Evaluation of various solvents

Solvent	% Product
DMAC	82.4
10% H_2O in DMAC	1.6
DMAC (under air)	8.5
DMF	76.9
1-methyl-2-pyrrolidinone (NMP)	77.3
Dioxane	69.5
THF	66.9
Toluene	23.0

Ethylene glycol dimethyl ether (DME)	60.8
Dimethyl sulfoxide (DMSO)	76.7
Propanenitrile [CuCl catalyst]	99
Acetonitrile [CuCl catalyst]	8
2-MeTHF [48 hr, CuCl catalyst]	98
BuOAc [24 hr, CuCl catalyst]	98
CPME [127 hr, with CuCl catalyst]	87
2-MeTHF/DMAC (4:1) [14-24 hr, CuCl catalyst]	98 -100

(Reactions are carried out in parallel reactors with 1.2 mmol 2,4-dichlorothiazole 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.25 mmol CuI, 0.25 mmol 1,10-phenanthroline and 2.1 mmol Cs_2CO_3 in 3 mL specified solvent. The reactions are degassed under N_2 for 30 minutes and then heated at 100°C overnight under N_2. Percent product is measured as the percent of total area under the HPLC curve for the product peak.)

Table 3: Evaluation of different copper sources

Copper Source	% Product
CuCl	81.3
CuBr	78.2
CuI	78.8

(Reactions are carried out in in parallel reactors with 1 mmol 2,4-dichlorothiazole 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.05 mmol CuX, 0.01 mmol 1,10-phenanthroline and 3 equivalents K_3PO_4 in 3 mL DMAC. The reactions are degassed under N_2 for 30 minutes and then heated at 100°C overnight under N_2. Percent product is measured as the percent of total area under the HPLC curve for the product peak.)

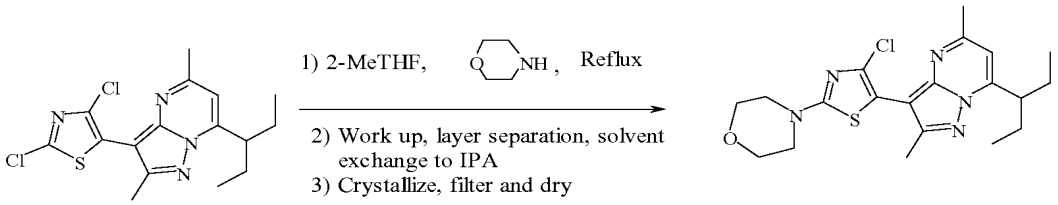
Table 4: Evaluation of various inorganic bases

Base	% Product
Cs_2CO_3	87.0
Cs_2CO_3 (1.1 eq.)	71.0
K_2CO_3	25.6
Na_2CO_3	6.0
Li_2CO_3	1.8
KOAc	5.3
K_3PO_4	83.8

(Reactions are carried out in in parallel reactors with 1 mmol 2,4-dichlorothiazole 1 mmol 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine, 0.1 mmol CuI, 0.1 mmol 1,10-phenanthroline and 2.1 mmol base and degassed for 30 minutes prior to the addition of 3 mL DMAC. The reactions are degassed under N_2 for 10 minutes and then heated at 100°C overnight under N_2. Percent product

is measured as the percent of total area under the HPLC curve for the product peak.)

Example 4. Use of morpholine both as a reactant and base in 2-MeTHF as solvent.



7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (15.2 g, 41.16 mmoles) is charged into a 250 mL 3-necked round bottomed flask, followed by addition of 2-MeTHF (61 mL, 4.0 volumes), the yellowish brown slurry is stirred at about 20 °C for 5 min. Then morpholine (19 g, 218.18 mmoles) is added over 2-5 minutes. Contents are heated to reflux and maintained at reflux for 12 hr. The slurry is cooled to 25 °C, followed by addition of 2-MeTHF (53 mL, 3.5 volumes) and water (38 mL 2.5 volumes). The reaction mixture is warmed to 40 °C, where upon a homogenous solution with two distinct layers formed. The layers are separated, the organic layer is filtered and concentrated to ~3 volumes at atmospheric pressure. Four volumes 2-propanol (61 mL) are added. The solution is concentrated to ~3 volumes followed by addition of 4 volumes 2-propanol (61 mL), re-concentrated to ~3 volumes, followed by addition of another 6 volumes 2-propanol (91 mL), and refluxed for 15 min. The clear solution is gradually cooled to 75 °C, seeded with 0.45 g 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine slurried in 2 mL 2-propanol, rinsed with an additional 2 mL 2-propanol and transferred to a crystallization flask. The slurry is cooled to between 0-5 °C, maintained for 1 hr, filtered and the product rinsed with 2-propanol (30 mL, 2 volumes). The solid is dried at 60 °C in a vacuum oven to afford 16.92 g 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine. Purity of product by HPLC assay is 100.00 %. XRPD and DSC data of product is consistant with reference sample. MS(ES) = 420 (M+1).

Example 5. Use of morpholine as both reactant and base in 2-propanol as solvent.

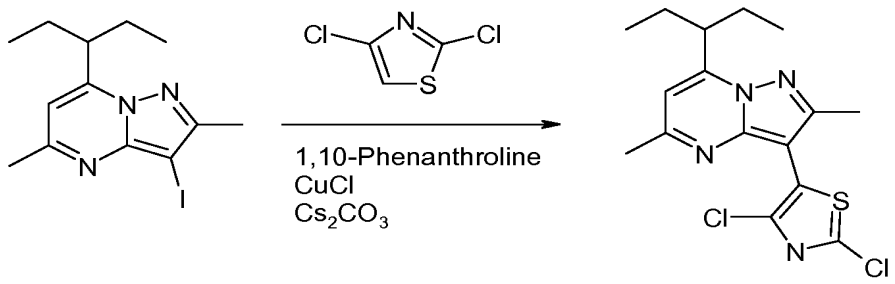
7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (11.64 mmoles) is charged into a 100 mL 3-necked round bottomed flask followed by addition of 2-propanol (16 mL, 3.72 volumes). The yellowish brown slurry is stirred at about 20 °C for 5 min. Then morpholine (3.3 g, 37.84 mmoles) is added over 2-5 minutes. Contents are refluxed for 6 hr. The slurry is cooled to 25 °C. 2-Propanol (32 mL, 7.44 volumes) and water (8.6 mL, 2.0 volumes) are added and the mixture warmed to 70-75 °C, filtered and concentrated to ~ 9 volumes at atmospheric pressure. The clear solution is gradually cooled to 55 °C, seeded with 0.06 g of crystalline 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine slurried in 0.5 mL 2-propanol, rinsed with additional 0.5 mL 2-propanol and added to crystallization flask. The slurry is cooled to 0-5 °C, maintained for 1 hr., filtered and the product rinsed with 2-propanol (9 mL, 2.1 volumes). Suctioned dried under vacuum at 60 °C to afford 4.6 g of dry 7-(1-ethyl-propyl)-3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (88.8 % yield, purity by HPLC assay is 99.88 %). MS(ES) = 420 (M+1).

Example 6: 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (10 g, 29.17 mmoles), 2, 4-dichlorothiazole (5.2 g , 33.76 mmoles), cesium carbonate(19.9g, 61.07 mmoles) and 1,10-phenanthroline (1 g, 5.5 mmoles) are charged into a 250 mL 3-necked round bottomed flask, followed by 2-MeTHF (36 mL, 3.6 volumes). The reaction mixture is degassed with nitrogen and then evacuated. Cuprous chloride (0.57 g, 5.7 mmoles), DMAC (10 mL, 1 volume) and 2-MeTHF (4 mL, 0.4 volumes) are added in succession. The reaction mixture is degassed with nitrogen and then evacuated. The contents are refluxed for 20 hr. The reaction mixture is cooled to ~70 °C and 2-MeTHF (100 mL, 10 volumes) is added. The contents are filtered at ~70 °C and the residual cake is washed with 2-MeTHF (80 mL, 8 volumes) at about 65-72°C. The filtrate is transferred into a separatory funnel and extracted with water. The organic layer is separated and washed with dilute HCl. The resulting organic layer is treated with Darco G60, filtered hot (60°C). The filtrate is concentrated at atmospheric pressure to ~2.8

volumes. 25 mL 2-propanol is added, followed by re-concentration to ~2.8 volumes. An additional 25 mL 2-propanol is added, followed again by re-concentration to ~2.8 volumes. Finally, 48 mL 2-propanol is added. The contents are cooled to -7 °C, maintained at -7 °C for 1 hr., filtered and rinsed with 20 mL chilled 2-propanol. Product is suction dried and then vacuum dried at 60 °C to afford 9.41 g 7-(1-ethyl-propyl)-3-(2,4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (purity of product by HPLC assay is 95.88 %). MS(ES) = 369 (M+1).

Example 7. Synthesis of 7-(1-ethyl-propyl)-3-(2, 4-dichloro-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine using 1,4-Dioxane solvent and CuCl catalyst



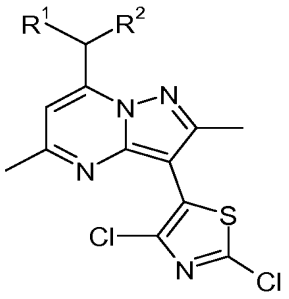
Add dioxane (9.06X), Cs_2CO_3 (2.00X), 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (1.0 equivalent), 2,4-dichlorothiazole (0.54 equivalent) to a reactor under N_2. Purge the reactor with N_2 three times, degas with N_2 for 0.5~1 hr., and then add 1,10-phenanthroline (0.3 eq) and CuCl (0.3eq) under N_2 , degassing with N_2 for 0.5~1 hr. Heat the reactor to 100 °C ~110 °C under N_2 . Stir the mixture for 22~24 hr. at 100 °C ~110 °C. Cool to 10~20°C and add water (10V) and CH_3OH (5V), stir the mixture for 1~1.5 hr. at 10~20°C. Filter the suspension, resuspend the wet cake in water, stirr for 1~1.5 hr. at 10~20°C, and filter the suspension again. Charge the wet cake to n-heptane (16V) and EtOAc (2V) under N_2. Heat the reactor to 40 °C~50 °C under N_2.

Active carbon (0.1X) is added at 40 °C~50 °C. The reactor is heated to 55°C~65 °C under N_2 and stirred at 55 °C~65 °C for 1~1.5 hr. The suspension is filtered at 40~55°C through diatomite (0.4 X). The cake is washed with n-heptane (2.5V). The filtrate is transferred to another reactor. EtOAc (10V) is added and the the organic layer washed with 2 N HCl (10V) three times, followed by washing two times with water (10X, 10V). The organic layer is concentrated to 3~4V below 50°C. The mixture is heated to

80~90 °C. The mixture is stirred at this temperature for 40~60 min. The mixture is cooled to 0~5°C, stirred for 1~1.5 hr. at 0~5°C and filtered. The cake is washed with n-heptane (1V) and vacuum dried at 45~50 °C for 8~10 hr. The crude product is dissolved in 2-propanol (7.5V) under N_2, and re-crystallized with 2-propanol. The cake is dried in a vacuum oven at 45°C~50°C for 10-12 hr. (55~80% yield). ^{1}H NMRδ6.537 (s, 1H) 3.591-3.659 (m, 1H, *J*=6.8Hz), 2.593 (s, 3H), 2.512 (s, 3H), 1.793-1.921(m, 4H), 0.885-0.903 (m, 6H).

WE CLAIM:

1. A compound of the formula



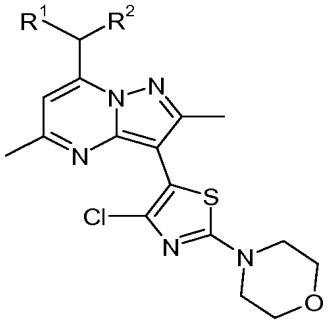
wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;

or a salt thereof.

2. The compound according to claim 1, or a salt thereof, wherein R^1 and R^2 are each ethyl.

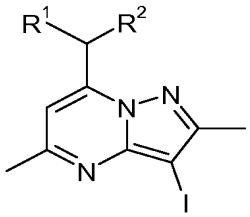
3. A synthetic process for preparing a compound of the formula



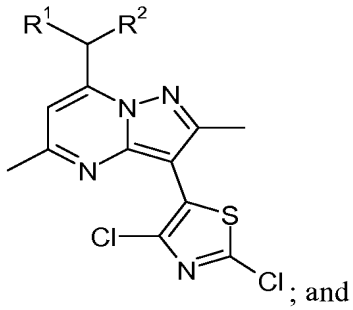
wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3, to form a compound of the formula



; and

ii) reacting the product of step i), with morpholine, or a salt thereof, in the presence of a suitable inorganic base.

4. The process according to Claim 3 wherein R^1 and R^2 are each ethyl.

5. The process according to either Claim 3 or Claim 4 wherein the copper halide is CuCl

6. The process according to any one of Claims 3-5 wherein the ligand is 1,10-phenanthroline.

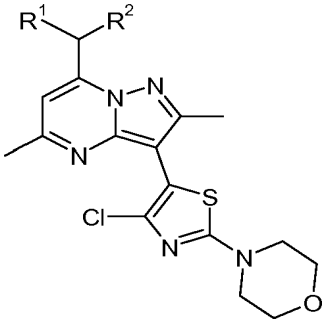
7. The process according to any one of Claims 3-6 wherein the base in step i) is Cs_2CO_3.

8. The process according to any one of Claims 3-7 wherein the base in step ii) is K_2CO_3.

9. The process according to claim 3 wherein R^1 and R^2 are each ethyl, the copper halide is CuCl, the ligand is 1,10-phenanthroline, the base in step i) is Cs_2CO_3, and the base in step ii) is K_2CO_3.

10. The process according to Claim 9 wherein the solvent for step i) is 1, 4-Dioxane or 2-MeTHF/DMAC and the solvent for step ii) is morpholine, 2-MeTHF, or 2-propanol

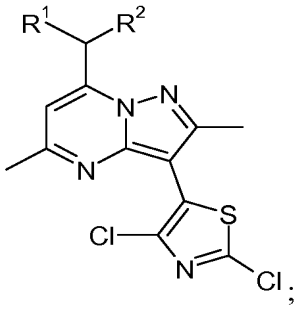
11. A synthetic process for preparing a compound of the formula



wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

i) reacting a compound of the formula



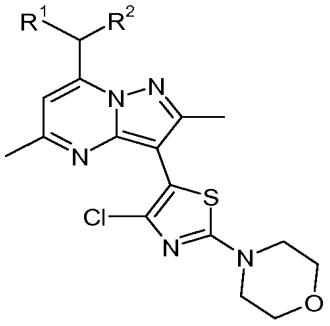
or a salt thereof, with excess morpholine or salt thereof, in the presence of a suitable solvent.

12. The process of Claim 11 wherein the solvent is 2-methyl tetrahydrofuran.

13. The process of Claim 11 wherein the solvent is 2-propanol.

14. The process of any one of Claims 11 – 13 wherein R^1 and R^2 are each ethyl.

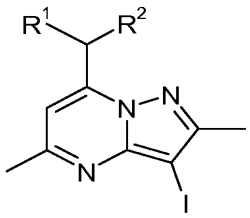
15. A synthetic process for preparing a compound of the formula



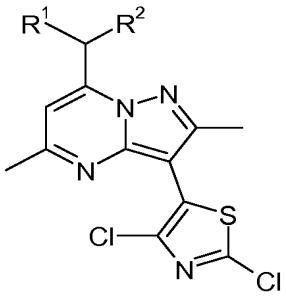
wherein R^1 and R^2 are independently ethyl or *n*-propyl,

comprising the steps of

i) reacting a compound of the formula



or a salt thereof, with 2,4-di-chlorothiazole, or a salt thereof, in the presence of a copper halide catalyst, a ligand selected from 1,10-phenanthroline and bipyridine, and a base selected from K_3PO_4 and Cs_2CO_3, to form a compound of the formula



; and

ii) reacting the product of step i), with an excess of morpholine, or a salt thereof, in in a suitable solvent.

16. The process of Claim 15 wherein the solvent is 2-methyl tetrahydrofuran.

17. The process of Claim 15 wherein the solvent is 2-propanol.

18. The process of any one of Claims 15 – 17 wherein R^1 and R^2 are each ethyl.

5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/058722

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/036579 A1 (LILLY CO ELI [US]; CHEN ZHAOGEN [US]; HAMDOUCHI CHAFIQ HAMDOUCHI [US];) 27 March 2008 (2008-03-27) cited in the application Pages 30-32, 36-38 examples 4,14,16,16/alternate preparation,17	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2010	25/01/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lange, Tim

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/058722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CR 10682 A	13-08-2009
		EA 200970303 A1	30-10-2009
		EP 2094709 A1	02-09-2009
		KR 20090052366 A	25-05-2009

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2020 (11.06.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/115555 A2

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/395* (2006.01)

(21) International Application Number:
PCT/IB2019/001325

(22) International Filing Date:
06 December 2019 (06.12.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/776,763 07 December 2018 (07.12.2018) US
62/816,674 11 March 2019 (11.03.2019) US

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(74) Agent: **BOYLE, Craig D.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
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(54) **Title:** CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

(57) **Abstract:** Provided are methods related to treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1 S)-2-cyclopropyl- 1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-l,3-thiazol-2-amine (Formula 1), or a pharmaceutically acceptable salt thereof. Further provided are pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(lS)-2-cyclopropyl-l-(3-fluoro-4-methylphenyl)ethyl]-5-mcthyl-N -prop-2 -ynyl-l,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

WO 2020/115555 A2

CRF1 RECEPTOR ANTAGONIST, PHARMACEUTICAL FORMULATIONS AND SOLID FORMS THEREOF FOR THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

TECHNICAL FIELD

The present disclosure relates to 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for the treatment of congenital adrenal hyperplasia (CAH). The present disclosure further relates to pharmaceutical formulations and solid forms of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and their use in the treatment of congenital adrenal hyperplasia (CAH).

BACKGROUND

Classic congenital adrenal hyperplasia (CAH) is a disease that includes a group of autosomal recessive disorders that result in an enzyme deficiency that alters the production of adrenal steroids due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., "An update to 21-hydroxylase deficient congenital adrenal hyperplasia," *Gynecol. Endocrinol.* (2010) 26(1):63-71; Hertzberg et al., "Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States," *J. Pediatr.* (2011) 159(4):555-560).

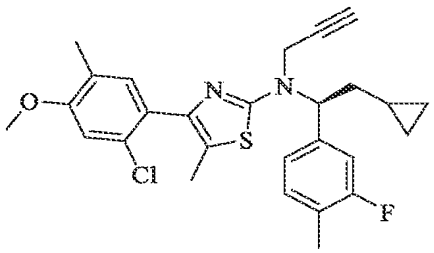
Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with

the greatest unmet medical need (Cheng and Speiser, "Treatment outcomes in congenital adrenal hyperplasia," *Adv. Pediatr.* (2012) 59(1):269-281; Merke and Poppas, "Management of adolescents with congenital adrenal hyperplasia," *Lancet Diabetes Endocrinol.* (2013) 1(4):341-352). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (e.g., hydrocortisone) and mineralocorticoids (e.g., fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and androgens (e.g., 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients.

Currently, exogenous corticosteroids are the standard of care for treating patients with classic CAH. This treatment is used to correct the cortisol deficiency and reduce the excessive ACTH levels and androgen excess. However, the dose and duration of steroid use required to suppress ACTH are typically well above the normal physiological level used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., "Bone mineral density in girls with classical congenital adrenal hyperplasia due to CYP21 deficiency," *J. Pediatr. Endocrinol. Metab.* (2008) 21(12):1155-1162; King et al., "Long-term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia," *J. Clin. Endocrinol. Metab.* (2006) 91(3):865-869; Migeon and Wisniewski, "Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Growth, development, and therapeutic considerations," *Endocrinol. Metab. Clin. North Am.* (2001) 30(1):193-206).

Corticotropin releasing factor (CRF) is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific corticotropin releasing factor 1 (CRF1) receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone.

The compound of Formula (I)



(I)

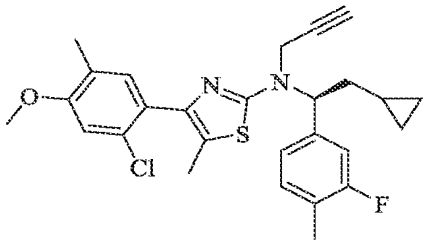
4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, is a selective CRF1 receptor antagonist. The compound of Formula (I) can be prepared according to the methods described in U.S. Patent Nos. 6,586,456 and 8,314,249, each of which is hereby incorporated by reference in its entirety. The compound of Formula (I) is a low solubility compound with low bioavailability. Partially due to its low solubility, attempts at formulating the compound of Formula (I) have proven to be difficult, particularly for formulations suitable for pediatric administration.

Thus, there is a need for a treatment for CAH that avoids the severe complications associated with corticosteroid therapy. There is also a need for a formulation of the compound of Formula (I) with increased bioavailability and a need for a formulation of the compound of Formula (I) that is suitable for pediatric administration. The formulations and methods of the present invention help address these and other needs.

SUMMARY

Provided herein is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



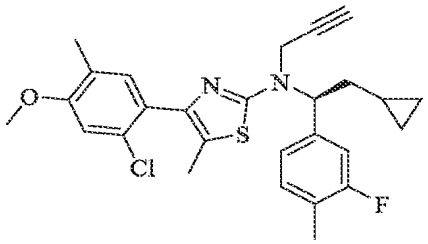
(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

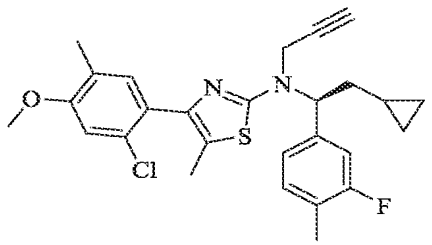
or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle.

Also provided herein is a pharmaceutical composition of the present disclosure (e.g., a pharmaceutical composition in oral solution dosage form of the present disclosure) for use in therapy, for example, for use in any of the methods disclosed herein.

Provided herein is a method for treating congenital adrenal hyperplasia (CAH) comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an

amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

In some embodiments, the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the circadian release occurs between the hours of 2 a.m. and 10 a.m.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject. In some embodiments, the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of androstenedione in the subject.

In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments, the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

Provided herein is a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-

1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

Provided herein is a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

Provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising

administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side

effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine,

or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the method comprises:

(i) measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

Provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method

of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject, wherein the subject is in a fed state.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1500 calories per liter with a caloric distribution of about 14.7% protein, about 32% fat and about 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

In some embodiments, administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-

N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

Provided herein is a method of reducing glucocorticoid burden in a subject as measured after a time period of administration of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is use of a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of reducing glucocorticoid burden in a subject, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Provided herein is a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, wherein the symptom is improved after a time period of administration of the compound , or pharmaceutically acceptable salt thereof, wherein the improvement in the

one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

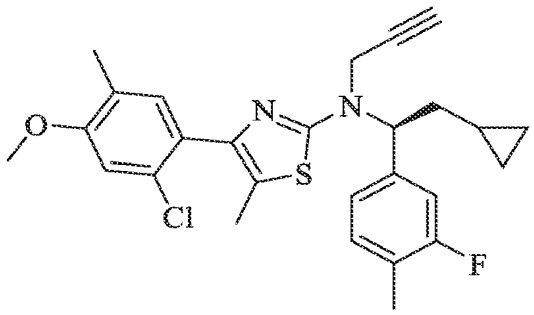
Also provided herein is a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is use of a compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of improving one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility in a subject having classic congenital adrenal hyperplasia, wherein the symptom is improved after a time period of administration of the compound, or pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound, or pharmaceutically acceptable salt thereof.

Also provided herein is a compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a spray-dried dispersion containing 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



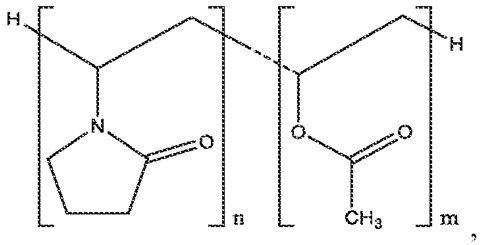
(I)

or a pharmaceutically acceptable salt thereof, and a polymer. In some embodiments, the polymer is selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:9 to about 1:1.

In some embodiments, the polymer is a neutral polymer. In some embodiment, the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

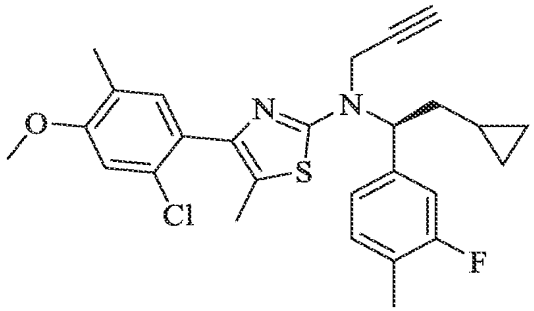
In some embodiments, the polymer is an enteric polymer. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

In some embodiments, the polymer is a pyrrolidone polymer. In some embodiments, the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA). In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight. In some embodiments, the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight. In some embodiments, the copolymer has the structure:



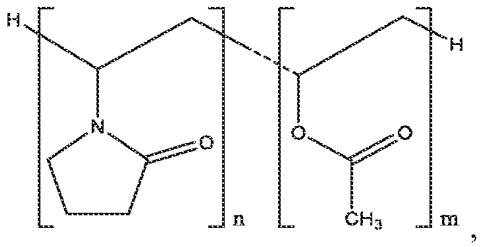
wherein the value of n is about 1 to about 2 times the value of m. In some embodiments, the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

Provided herein is a spray-dried dispersion comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

In some embodiments of the spray-dried dispersions of the present disclosure, the compound of Formula (I) and the polymer together form homogeneous particles. In some embodiments, the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 10 μm to

about 50 μm. In some embodiments, the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm.

In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

In some embodiments, the particles have a residual solvent content less than about 2 wt %. In some embodiments, the particles have a residual solvent content less than about 1 wt %. In some embodiments, the particles have a residual solvent content of about 0.5 wt % or less.

In some embodiments, the compound of Formula (I) in the dispersion is substantially amorphous.

Also provided herein is a method for preparing a spray-dried dispersion of the present disclosure, comprising: dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

In some embodiments, the method comprises removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion. In some embodiments, the spray-dried dispersion is dried with a convection tray dryer. In some embodiments, the organic solvent is acetone.

In some embodiments, the spray dryer inlet temperature is about 60°C to about 80°C. In some embodiments, the spray dryer inlet temperature is about 72°C.

In some embodiments, the spray dryer outlet temperature is about 25°C to about 45°C. In some embodiments, the spray dryer outlet temperature is about 35°C.

In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.2 g/mL. In some embodiments, the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.3 g/mL. In some embodiments, the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

Also provided herein is a pharmaceutical composition comprising the spray-dried dispersion of the present disclosure and one or more pharmaceutically acceptable excipients. In some embodiments, the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition. In some embodiments, the spray-dried dispersion is present in an amount of about 40% to 80% w/w of the composition.

In some embodiments, the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

In some embodiments, the pharmaceutical composition is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the pharmaceutical composition is coated.

In some embodiments, the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

Also provided herein is a method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of the present disclosure with one or more pharmaceutically acceptable excipients.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective

amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state. In some embodiments, the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

In some embodiments, administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

In some embodiments of the disclosed methods, the subject is a pediatric subject.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of a spray-dried dispersion of the present disclosure for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Also provided herein is a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

Also provided herein is pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for manufacture of a medicament for use in any of the methods disclosed herein.

Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving gastrointestinal absorption of

a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

In some embodiments, the subject is a pediatric subject.

Also provided herein is a method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject a therapeutically effective amount of a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is a spray-dried dispersion of the present disclosure or a pharmaceutical composition comprising a spray-dried dispersion of the present disclosure, for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

Also provided herein is use of a spray-dried dispersion of the present disclosure in the manufacture of a medicament for use in a method of improving oral bioavailability of a compound of Formula (I) in a subject, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

In some embodiments, the subject is a pediatric subject.

Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

Also provided herein is a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for use in therapy, for example, for use in any of the methods disclosed herein.

Also provided herein is use of a crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt, for manufacture of a medicament for use in any of the methods disclosed herein.

Other features and advantages of the methods, processes, formulations, and uses provided herein will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 shows the dissolution performance of several spray-dried dispersion formulations in 0.5 wt% simulated intestinal fluid (SIF) in phosphate buffered saline (PBS), pH 6.5.

FIG. 2 shows the vertical membrane flux cell integrated in the μDiss Profiler™ used for the membrane flux assay.

FIG. 3 shows non-sink dissolution data for several spray-dried dispersion formulations and the compound of Formula (I) in 0.5 wt% SIF in PBS, pH 6.5.

FIG. 4 is a graph showing membrane flux of 1 mg/mL GB/IB 0.5 wt% SIF doses of the compound of Formula (I) and various spray-dried dispersion formulations over time. The solid lines indicate flux ($\mu g\ min^{-1}\ cm^{-2}$) and the broken lines indicate concentration (μg/mL) in 0.5% SIF.

FIG. 5 is a flow diagram of the spray drying manufacturing process used to prepare a 1000 g batch of a SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64.

FIGS. 6A and 6B are line graphs showing the pharmacokinetic results of a bioavailability and food effect study in dogs. FIG. 6A shows the results from Cohort 1 and FIG. 6B shows the results from Cohort 2.

FIG. 7 is a flow chart showing the study design of a Phase 1 study of the pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIGS. 8A and 8B are line graphs showing the mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions, respectively, in healthy adult subjects.

FIGS. 9A-9C are spaghetti plots of the pharmacokinetics of the compound of Formula (I) in healthy adult subjects under fasted and fed conditions. FIG. 9A shows the $AUC_{0\text{-tlast}}$ values. FIG. 9B shows the $AUC_{0\text{-}\infty}$ values. FIG. 9C shows the C_{max} values.

FIG. 10 is a flow chart showing the study design of a Phase 1 study of the bioavailability, pharmacokinetics and food effect of the compound of Formula (I) in healthy adult subjects.

FIG. 11 shows the study design of a Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia.

FIGs. 12A and 12B show the arithmetic mean values for adrenocorticotropic hormone (ACTH) (FIG. 12A) and 17-hydroxyprogesterone (17-OHP) (FIG. 12B) for all 8 Cohort 1 subjects plotted at each time point for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 13A and 13B show arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for pre-treatment baseline (circles), day 1 (squares), and day 14 (triangles).

FIGs. 14A and 14B show the reduction of ACTH at timepoints 8-, 10-, and 12-hours postdose. FIG 14A shows the values for each time point as compared to baseline. FIG. 14B shows the mean values across all three timepoints.

FIGs. 15A and 15B show the reduction of 17-OHP at timepoints 8-, 10-, and 12-hours postdose. FIG 15A shows the values for each time point as compared to baseline. FIG. 15B shows the mean values across all three timepoints.

FIGs. 16A and 16B show the reduction of androstenedione at timepoints 8-, 10-, and 12-hours postdose. FIG 16A shows the values for each time point as compared to baseline. FIG. 16B shows the mean values across all three timepoints.

FIG. 17A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 17B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 17C: shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 50 mg Dose qhs (Cohort 1; n=8). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 18A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard

error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 18B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 18C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose qhs (Cohort 2; n=4). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 19A shows the plasma ACTH Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. ACTH normal ranges: Female 6 to 58 pg/mL; Male 7 to 69 pg/mL.

FIG. 19B shows the serum 17-OHP Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. 17-OHP normal ranges: Female < 207 ng/dL; Male < 139 ng/dL.

FIG. 19C shows the serum Androstenedione Mean Blood Concentrations following the compound of Formula (I) 100 mg Dose with Evening Meal (Cohort 3). Error bars represent the standard error of the mean for each morning window timepoint. Androstenedione normal ranges: Female 26 to 214 ng/mL; Male 33 to 134 ng/mL.

FIG. 20 is a scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIG. 21 is an alternative scheme showing the manufacturing process for forming 50 mg capsules of the compound of Formula (I).

FIGs. 22A and 22B show a scheme showing the manufacturing process for forming SDD granules of the compound of Formula (I).

FIG. 23 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 1 of the compound of Formula (I).

FIG. 24 is a scheme showing the manufacturing process for forming 50 mg/nL liquid formulation 2 of the compound of Formula (I).

FIG. 25 is an XRPD spectrum of the compound of Formula (I) free base crystalline form I.

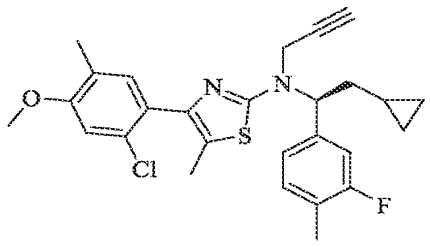
FIG. 26 is a DSC spectrum of the compound of Formula (I) free base crystalline form I.

FIG. 27 is an XRPD spectrum of the compound of Formula (I) tosylate crystalline form 1.

FIG. 28 is a DSC and TGA spectrum of the compound of Formula (I) tosylate crystalline form 1.

DETAILED DESCRIPTION

As described herein, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine having the Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, is a selective CRF1 receptor antagonist that has been found to be effective treating congenital adrenal hyperplasia. Specifically, the compound of Formula (I) has been found to effectively reduce several biomarkers associated with congenital adrenal hyperplasia.

Newborn screening for CAH is performed by immunoassay to measure 17-OHP levels in heel-stick capillary blood specimens obtained within the first 72 hours of life. The blood sample is analyzed for 17-OHP by commercially available dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA; PerkinElmer, Waltham Massachusetts) (White et al., *J. Pediatr.* 163:10-12 (2013)). Second-tier screening tests utilizing biochemical and molecular genetic testing methods, performed between 8 and 14 days of life, are employed by nine states in the United States and strongly recommended by an additional 5 states. The biochemical method includes immunoassay with organic solvent extraction or liquid chromatography followed by tandem mass spectrometry to measure steroid ratios of 17-OHP, androstenedione, and 21-deoxycortisol to cortisol (*see, e.g.,* Speiser et al., *Int. J. Pediatr. Endocrinol.* 2010:494173,

2010). The genetic screen looks for *CYP21A2* mutations that are associated with CAH. While not widely employed in the U.S., the addition of a second screening could potentially improve the sensitivity of the overall screening process, where sensitivity of the first screen alone is approximately 72%.

In absence of results from the newborn screening, female infants with classical CAH are typically identified due to the presence of ambiguous genitalia. Males have normal genitalia at birth and therefore are not diagnosed unless newborn screening is conducted or other medical complications come to attention. Infants who are not initially diagnosed with CAH and suffer from the salt-wasting form of the disease are later diagnosed in the setting of poor weight gain, vomiting, hyperkalemia and hyponatremia within the first few weeks of life.

Treatment of CAH is based on normalization of hormone and steroid levels using a variety of medications from diagnosis in infancy through adulthood. Glucocorticoids are the current standard treatment in CAH and are used both to correct the endogenous cortisol deficiency and for reducing the elevated ACTH levels from the pituitary, which drives increased androgen production. Unlike the treatment of Addison's disease (adrenal insufficiency), in which cortisol replacement is sufficient, the treatment of CAH must also reduce ACTH production, to control the subsequent androgen excess as well. Thus, the goals of glucocorticoid treatment include cortisol replacement and suppression of ACTH to prevent virilization and menstrual disturbances in women and to inhibit testicular adrenal rest tumors in men. Mineralocorticoid replacement is needed to achieve normal plasma renin activity for maintenance of regular blood pressure, electrolyte balance, and volume status in those patients with the salt-wasting form of CAH.

The regimen of glucocorticoid treatment must support normal physiology and also ensure that sufficient cortisol is available during events that may elicit a strong stress response (*e.g.,* intercurrent illness, exercise, hypotension). Careful monitoring is also necessary to avoid the development of iatrogenic Cushing's syndrome due to glucocorticoid overtreatment in an effort to adequately suppress androgen production, or Addisonian syndrome due to under-treatment.

Overtreatment with mineralocorticoids may cause hypertension while under-treatment may lead to low blood pressure, salt loss, fatigue and increased requirements for glucocorticoids. Typical laboratory tests for monitoring treatment efficacy include measurement of plasma concentrations of 17-OHP, androstenedione, testosterone, renin activity, and electrolytes.

Adult patients with CAH have an increased prevalence of risk factors for cardiovascular disease including obesity, hypertension, and insulin resistance (*see, e.g.,* Kim et al., *Semin. Reprod. Med.* 27(4):316-21 (2009)). A study of a large cohort of pediatric and adult CAH patients (n=244) demonstrated that patients are prescribed a variety of glucocorticoid treatment regimens yet frequently suffer from poor hormonal control and the aforementioned adverse outcomes (*see, e.g.,* Finkielstain et al., *J. Clin. Endocrinol Metab.* 97(12):4429-38 (2012)).

Treatment of CAH includes efforts to normalize the cortisol deficiency with glucocorticoids (usually hydrocortisone in children but often more potent agents with narrow therapeutic indices, such as dexamethasone, in adults) and, if necessary for salt-wasting, mineralocorticoids (usually fludrocortisone). The glucocorticoid doses required to achieve sufficient suppression of excess androgens, however, are usually well above the normal physiologic dose used for cortisol replacement alone as in patients with Addison's disease. This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, and decreased bone mineral density in CAH patients (*see, e.g.,* Elnecave et al., *J. Pediatr. Endocrinol. Metab.* 21:1155-62 (2008); King et al., *J. Clin. Endocrinol. Metab.* 91(3):8656-59 (2006); Migeon et al., *Endocrinol. Metab. Clin. North Am.* 30:193-206 (2001)). Recently, best practices for the clinical management of congenital adrenal hyperplasia were published in the *Journal of Clinical Endocrinology and Metabolism* (Speiser, P.W., et al. *J. Clin. Endocrinol. Metab.* November 2018, 103(11): 1-46). This article is incorporated by reference in its entirety.

Corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide. CRF has been found to produce profound alterations in endocrine, nervous, and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-induced release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (*see, e.g.,* Vale et al., *Science 213*:1394-1397, 1981). Secretion of CRF causes release of ACTH from corticotrophs in the anterior pituitary via binding to the CRF_1 receptor, a member of the class B family of G-protein coupled receptors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF_1 receptor binding activity and which are capable of antagonizing the CRF_1 receptor remains a desirable goal and has been the subject of ongoing research and development for the treatment of anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, and substance abuse.

The pituitary hormone ACTH, under the control of hypothalamic corticotropin-releasing factor (CRF), stimulates uptake of cholesterol and drives the synthesis of pregnenolone initiating steroidogenesis in the adrenal gland. The adrenal cortex is comprised of three zones, which produce distinct classes of hormones many of which are driven by ACTH mobilizing cholesterol through this pathway. Deficiencies in these enzymes as a result of mutation or deletion cause the substrate concentrations to increase. In the most common form of CAH resulting from mutations or deletions in the 21-hydroxylase gene (CYP21A2), potent androgens are produced by the adrenal because of the accumulation of the steroid precursors, progesterone and 17-hydroxyprogesterone (17-OHP). Plasma levels of 17-OHP can reach 10-1000 times the normal concentration in these cases. These increases result in the overproduction of androgens, specifically androstenedione, testosterone, and dihydroxytestosterone causing virilization in females. In addition, 21-hydroxylase deficiency in CAH causes insufficient biosynthesis of glucocorticoids and mineralocorticoids, specifically cortisol and aldosterone. Cortisol is a critical negative feedback regulator of hypothalamic CRF secretion and pituitary ACTH release. The lack of glucocorticoid synthesis and release eliminates the restraint on the hypothalamus and pituitary, which causes ACTH levels to increase. The excessive ACTH stimulation causes hypertrophy of the zona fasciculata and zona reticularis resulting in adrenal hyperplasia.

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

The term "about" preceding a value for DSC, TGA, or T_g, which are reported as degrees Celsius, have an allowable variability of ±5°C. In all other instances, unless otherwise specified, the term "about" preceding a stated value includes the stated value and also includes ±20% of the stated value, and includes more specifically values of ±10%, ±5%, ±2%, and ±1% of the stated value.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

"Room temperature" or "RT" refers to the ambient temperature of a typical laboratory, which is typically around 25°C.

"Spray-drying" refers to the method of producing a dry powder from a solution or slurry. The solution or slurry is atomized or rapidly dried with a hot gas, e.g., air or nitrogen, that causes the solvent to evaporate quickly and uniformly. A "spray-dried dispersion" refers to the powder obtained from the spray-drying process.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, co-solvents, complexing agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, which are not biologically or otherwise undesirable. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the formulations. In addition, various excipients, such as are commonly used in the art, can be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman *et al.* (Eds.) (2010); *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, 12th Ed., The McGraw-Hill Companies.

"Subject," as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate. In some embodiments, the subject is a human.

In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having congenital adrenal hyperplasia (CAH). In some embodiments, the subject is suspected of having CAH. In some embodiments, the subject has a clinical record indicating that the subject has CAH (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the subject is a pediatric subject.

The term "pediatric subject" as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman et al., *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph et al., *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery et al., *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

As used herein, the terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing," as used herein, means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical formulation to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian. The preferred method of administration can vary

depending on various factors, e.g., the components of the pharmaceutical formulation, the site of the disease, and the severity of the disease.

As used herein, "therapeutically effective amount" is an amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an amount of a pharmaceutical composition comprising the compound of Formula (I), which is sufficient to achieve the desired effect and can vary according to the nature and severity of the disease condition, and the potency of the compound. A therapeutic effect is the relief, to some extent, of one or more of the symptoms of the disease, and can include curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease can exist even after a cure is obtained (such as, e.g., extensive tissue damage).

The term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or unit cell and consequently have no definable long range ordering. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), or other standard techniques known to those of skill in the art.

As used herein, "time of day window" refers to a period of time defined by a window start time and a window stop time. These times all refer to local times where a sample was taken. The phrase "same time of day window" when referring to samples taken from the subject mean, e.g., that a sample taken at 8:15 a.m. and a sample taken at 9:15 a.m. are considered to be taken in the same time of day window of, e.g., 2 a.m. to 10 a.m. or 6 a.m. to 10 a.m.

Methods

The present disclosure relates to methods of treating congenital adrenal hyperplasia (CAH). The methods include administering to a subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Provided herein is a method of treating congenital adrenal hyperplasia (CAH) comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof to normalize or partially normalize levels of biomarkers associated with congenital adrenal hyperplasia. In some embodiments, normalizing or partially normalizing levels of biomarkers comprises reducing levels of elevated biomarkers or increasing levels of depressed biomarkers as compared to subject without CAH.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers associated with congenital adrenal hyperplasia. In some embodiments, the biomarkers are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

In some embodiments, the reduction in level of any of the biomarkers (e.g., any of 17-OHP, ACTH, and androstenedione) is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. A day prior to administering the compound of Formula (I) applies to a subject that has not previously been administered the compound of Formula (I) within at least the past 24 hours.

In some embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 2 a.m. and 10 a.m. In other embodiments, the circadian release of biomarkers associated with CAH occurs between the hours of 6 a.m. and 10 a.m.

In some embodiments of any of the methods disclosed herein, the compound of Formula (I), or a pharmaceutically acceptable salt, is administered to the subject at nighttime or administration prior to sleep (i.e., bedtime administration). In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered six to eight hours prior to the circadian release of the biomarker. Administration prior to the circadian release may be adapted for shift workers (*e.g.*, those who work at night and sleep during the day), in which case administration will not necessarily occur at nighttime. Administration is

therefore dependent upon the expected circadian release of the biomarker, and can vary depending upon the individual's (*i.e.*, subject, patient) particular work and sleep patterns.

In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25%. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50%. In some embodiments of the methods provided herein, the level of 17-hydroxyprogesterone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of 17-hydroxyprogesterone is reduced to a level within the range of 17-hydroxyprogesterone expected for a subject without CAH, i.e., less than 1,000 ng/dL or less than 200 ng/dL.

In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50%.

In some embodiments of the methods provided herein, the level of adrenocorticotropic hormone is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of adrenocorticotropic hormone is reduced to a level within the range of adrenocorticotropic hormone expected for a subject without CAH.

In some embodiments of the methods provided herein, the level of androstenedione is reduced by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at lease 35%, at least 40%, at least 50%, at least 55% or at least 60% from pre-administration levels. In some embodiments, the level of androstenedione is reduced by at least 25%. In some embodiments,

the level of androstenedione is reduced by at least 30%. In some embodiments, the level of androstenedione is reduced by at least 50%.

In some embodiments of the methods provided herein, the level of androstenedione is reduced by an amount of from about 10% to about 90%, about 15% to about 90%, about 20% to about 90%, about 25% to about 90%, about 30% to about 90%, about 35% to about 90%, about 40% to about 90%, about 50% to about 90%, about 55% to about 90%, or about 60% to about 90% from pre-administration levels.

In some embodiments, the level of androstenedione is reduced to a level within the range of androstenedione expected for a subject without CAH, i.e., less than 200 ng/dL.

Also provided herein is a method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce one or more biomarker of CAH in a subject, e.g. reduce the androstenedione in the subject. Growth impairment can refer to, e.g., accelerated height velocity, accelerated weight velocity, and/or accelerated bone age.

Provided herein is a method for reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

Provided herein is a method for reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the corticosteroid is a glucocorticoid.

Also provided herein is a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The long-term effects of glucocorticoid treatment are well documented in the art (see, e.g., Oray, M. et al. (2016): Long-term effect of glucocorticoids, *Expert Opinion on Drug Safety*. DOI: 10.1517/14740338.2016.1140743). Such side effects are associated with every biological system, e.g., musculoskeletal (e.g., osteoporosis, avascular necrosis of bone, and

myopathy), endocrine and metabolic (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression), gastrointestinal (e.g., gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis), cardiovascular (e.g., hypertension, coronary heart disease, ischemic heart disease, heart failure), dermatologic (e.g., dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, and hair loss), neuropsychiatric (e.g., mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, and delirium), ophthalmologic (e.g., cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, and central serous chorioretinopathy), and immunologic (e.g., suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections).

Accordingly, in some embodiments, the side effects of glucocorticoid treatment are selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, reactivation of latent infections, and any combination thereof.

Provided herein is a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii)administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

In some embodiments, the method further comprises (iv) measuring the level of the one or more biomarkers after administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i). In some embodiments, the method further comprises (v) continuing the administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m. In some embodiments, steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

In some embodiments, steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

In some embodiments, step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

In some embodiments, step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

In some embodiments of the methods of the present disclosure, the compound of Formula (I) is administered at an amount equivalent to from about 25 mg to about 150 mg of the compound of Formula (I) free base. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at an amount equivalent to about 50 mg or about 100 mg of the compound of Formula (I) free base.

In some embodiments of the methods disclosed herein, compound of Formula (I) is administered in the free base form.

In some embodiments of the methods disclosed herein, the compound of Formula (I) is administered once daily.

Also provided herein is a method of treating CAH in a pediatric subject. The methods include administering to a pediatric subject a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of a SDD of the present disclosure that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes administering to a pediatric subject a therapeutically effective amount of pharmaceutical composition of the present disclosure that contains a SDD that includes a polymer and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pediatric subject is a neonate. In some embodiments, the pediatric subject is an infant. In some embodiments, the pediatric subject is a child. In some embodiments, the pediatric subject is an adolescent.

In some embodiments of the methods of the present disclosure, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject in a fed state. The term "fed state," as used herein, refers to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof from about 1 hour before consumption of food or a nutritional composition to about 1 hour after consumption of food or a nutritional composition. The term "fasted state," as used herein, refers to a gap of at least two hours between consumption of food or a nutritional composition and administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with food or a nutritional composition, such as a nutritional supplement or formula, a meal replacement beverage, a liquid dietary supplement, or a high caloric liquid meal. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour before the subject has consumed food or a nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject within about 1 hour after the subject has consumed food or a nutritional composition. Examples of suitable nutritional compositions include, but are not limited to, infant formulas, dietary supplements, dietary substitutes, and rehydration compositions. In some embodiments, the food is a product containing concentrated calories and protein. In some embodiments, the nutritional composition is a composition utilized for enteral and parenteral supplementation for infants, specialty infant formulas, supplements for the elderly, and supplements for those with

gastrointestinal difficulties and/or malabsorption. Adult and pediatric nutritional formulas are well known in the art and are commercially available (e.g., Similac®, Ensure®, Jevity® and Alimentum® from Ross Products Division, Abbott Laboratories, Columbus, Ohio).

In some embodiments, the nutritional composition is in liquid form. The energy density of the nutritional compositions, when in liquid form, can range from about 0.6 Kcal to about 3 Kcal per mL. In some embodiments, the nutritional composition is in solid or powdered form. When in solid or powdered form, the nutritional supplements can contain from about 1.2 to more than 9 Kcals per gram, such as about 3 to 7 Kcals per gram.

In some embodiments, the nutritional composition is a meal replacement bar. Examples include PowerBar®, Glucerna® bars, Choice DM® bars, Ensure® bars, and Boost® bars. In some embodiments, the nutritional composition is a nutrition shake or meal replacement beverage. Commercially available examples include the Ensure® branded adult products (such as Ensure® Original, Ensure® Plus, Ensure® Enlive, Ensure® High Protein, Ensure® Clear, and Ensure® Light), Glucerna®, Choice DM®, Slim Fast®, Pediasure®, Glytrol®, and Resource®. In some embodiments, the nutritional composition is Ensure® Plus. In some embodiments, the nutritional composition is vanilla-flavored Ensure® Plus. Ensure Plus® is a high calorie liquid dietary supplement that contains 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments of the methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject before administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject at the same time as administration of the nutritional composition.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to the subject, followed by administration of the nutritional composition. In some embodiments, the nutritional composition is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60

minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the nutritional composition is administered within 30 minutes of administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments, the nutritional composition is administered to the subject, followed by administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered about 1 minute, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, or about 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered 1 minute, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, or 60 minutes, or within a range defined by any of the preceding values after administration of the nutritional composition. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered within 30 minutes of administering the nutritional composition. In some embodiments of the disclosed methods, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered to the subject with 8 fluid ounces (237 mL) of Ensure® Plus. In some embodiments, the Ensure® Plus is vanilla-flavored.

In some embodiments of the methods, a food effect is observed between administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a fed state versus a fasted state. The term "food effect," as used herein, refers to the relative difference in AUC (area under the curve $AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or C_{max} (maximum plasma concentration or peak plasma concentration) of an active substance, when the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered orally to a subject, concomitantly with

food or in a fed state as compared to the same values when the same compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in a fasted state. The food effect (F) is calculated as:

$$F\% = [(X_{fasted} - X_{fed}) / X_{fasted}] \times 100$$

where X_{fed} and X_{fasted} are the values of AUC ($AUC_{(0-t)}$ and/or $AUC_{(0-\infty)}$) or C_{max} in the fed and fasted state, respectively. In some embodiments, an increased, or positive, food effect is observed when the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered to a subject in a fed state. In some embodiments, administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in an increased, or positive, food effect, whereby an increased C_{max} and/or AUC are observed when administered orally in the fed state as compared to the fasting state.

In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is about 10 to about 20.

In some embodiments of the methods, the ratio of the AUC in the fed state to the AUC in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the AUC in the fed state to the AUC in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values.

In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10, such as about 5 to about 9, about 5 to about 8, about 5 to about 7, about 5 to about 6, about 6 to about 10, about 6 to about 9, about 6 to about 8, about 6 to about 7, about 7 to about 10, about 7 to about 9, about 7 to about 8, about 8 to about 10, about 8 to about 9, or about 8 to about 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5, about 6, about 7, about 8, about 9, or about 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 1.5

to about 3 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5 to 10, such as 5 to 9, 5 to 8, 5 to 7, 5 to 6, 6 to 10, 6 to 9, 6 to 8, 6 to 7, 7 to 10, 7 to 9, 7 to 8, 8 to 10, 8 to 9, or 8 to 10. In some embodiments, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is 5, 6, 7, 8, 9, or 10, or within a range defined by any of the preceding values. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is 1.5 to 3 times higher in the fed stated compared to the fasted state. In some embodiments, the mean C_{max} of the compound of Formula (I), or pharmaceutically acceptable salt thereof, is about 2 times higher in the fed stated compared to the fasted state. In some embodiments of the methods, the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 10 to about 20.

In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a meal. In some embodiments, the meal is a high fat, high caloric meal. In some embodiments, the meal is a low fat, low caloric meal. In some embodiments, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered within approximately 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

In some embodiments, the fed state is with a high fat meal. In some embodiments, the fed state is with a low fat meal. The FDA has provided draft guidelines regarding high fat and low fat meals ("Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations Guidance for Industry," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2019, Clinical Pharmacology). Table 1 shows test meal definitions provided by the FDA guidance.

Table 1

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat	800-1000	500-600	55-65	50
Low-Fat	400-500	100-125	11-14	25

The composition of a high fat meal provided by the FDA guidance is depicted in Table 2.

Table 2. Composition of a High Fat Meal*

Total Calories	800-1000
Calories from Protein	150
Calories from Carbohydrates	250
Calories from Fat	500-600
An Example of a High Fat Breakfast	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk

*50 percent of calories are derived from fat. Substitutions can be made to this meal, if the content, volume, and viscosity are maintained.

The composition of a low fat meal provided by the FDA guidance is depicted in Table 3.

Table 3. Composition of a Low Fat Meal

Total Calories	400-500
Fat (g)	250
Percent Calories from Fat	25
An Example of a Low Fat Breakfast*	• Eight ounces milk (1 percent fat) • One boiled egg • One packet flavored instant oatmeal made with water

*This low-fat breakfast contains 387 calories and has 10 grams of fat.

In some embodiments, a high fat meal contains 800-1000 total Kcal and 500-600 fat Kcal. In some embodiments, a low fat meal contains 400-500 total Kcal and 100-125 fat Kcal.

Also provided herein is a method of improving gastrointestinal absorption of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion. In some embodiments, the subject is a pediatric subject.

Also provided herein is a method of improving oral bioavailability of a compound of Formula (I), or pharmaceutically acceptable salt thereof, in a subject. The method includes orally administering to the subject a pharmaceutical composition of the present disclosure, wherein the improvement is relative to oral administration of the compound of Formula (I), or pharmaceutically acceptable salt thereof, which has not been prepared as a spray-dried dispersion.

In some embodiments of the methods provided herein, the subject is a pediatric subject.

Also provided herein is a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the present disclosure, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition is a lipidic semi-solid formulation. In some embodiments, the pharmaceutical composition is a liquid formulation. In some embodiments, the pharmaceutical composition is administered to the subject in a fed state.

Also provided herein is a pharmaceutical composition of the present disclosure for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject. In some embodiments, the subject is in a fed state.

In some embodiments, the pharmaceutical composition is administered to the subject with a nutritional composition. In some embodiments, the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%. In some embodiments, the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate. In some embodiments, the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces. In some embodiments, the nutritional composition is administered in an amount of about 8 fluid ounces. In some embodiments, the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

In some embodiments, the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is

1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

In some embodiments, the subject is a pediatric subject.

In some embodiments, the pharmaceutical composition is formulated for oral administration and exhibits a positive food effect when administered orally. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 10 to about 20. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4 or 5 to 10. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1 to 4. In some embodiments, the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of 1.5 to 3. In some embodiments, the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of 1.5 to 3.

In some embodiments, the pharmaceutical composition is administered to the subject with a meal. In some embodiments, the meal is a high fat meal. In some embodiments, the meal is a low fat meal. In some embodiments, the pharmaceutical composition is administered

within about 5 minutes after the start of the meal. In some embodiments, the meal is an evening meal. In some embodiments, the meal is a morning meal.

In some embodiments, administering the pharmaceutical composition exhibits a positive food effect. In some embodiments, the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 10 to about 20. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4 or 5 to 10. In some embodiments, the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1 to 4. In some embodiments, the ratio of the AUC of the compound

of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is 1.5 to 3. In some embodiments, the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is 1.5 to 3.

For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

Reduction in glucocorticoid burden, adrenal androgens and precursors

Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are corticosteroids that bind to the glucocorticoid receptor that is present in almost every vertebrate animal cell. In some embodiments, the subject is concurrently receiving a dose of a glucocorticoid. In some embodiments, the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate. In some embodiments, the glucocorticoid is cortisol (hydrocortisone). In some embodiments, the glucocorticoid is cortisone. In some embodiments, the glucocorticoid is prednisone. In some embodiments, the glucocorticoid is dexamethasone.

In some embodiments, the glucocorticoid dose is measured in hydrocortisone equivalents. In some embodiments, the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents. Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing.

In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically

acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose concurrently given to the subject is a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2 to about 16 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 5 to about 11 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 6 to about 10 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 7 to about 9 mg/m^2/day. In

some embodiments, a normal physiological dose of hydrocortisone equivalents is about 4 to about 9 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 12 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is less than about 8 mg/m^2/day. In some embodiments, a normal physiological dose of hydrocortisone equivalents is about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15 or about 16 mg/m^2/day, or within a range defined by any of the preceding values.

In some embodiments, the glucocorticoid dose concurrently given to the subject is at the upper limit of normal of a normal physiological dose of hydrocortisone equivalents. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose concurrently given to the subject is determined after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the upper limit of normal is 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2 times the normal physiological dose. In some embodiments, the upper limit of normal is about 2.5 times the normal physiological dose. In some embodiments, the upper limit of normal is about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, or about 3.0 times the normal physiological dose, or within a range defined by any of the preceding values.

In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the

glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period

of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the glucocorticoid dose of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction

of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 40%

after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time

period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of adrenocorticotropic hormone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of androstenedione is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt

thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of androstenedione of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of testosterone is reduced by at least 25% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 30% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of testosterone of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50% after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than 1.5 times the upper limit of normal and the level of androstenedione is less than 1.5 times the upper limit of normal after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal

limits and the level of androstenedione is within normal limits after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the level of 17-hydroxyprogesterone and androstenedione of the subject is reduced within a range defined by any of the preceding values.

In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition comprising the compound of

Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) in the subject is improved after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the improvement in the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is relative to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) results prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fatigue is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in fatigue is relative to the fatigue prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, sleep is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in sleep is relative to the sleep prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, insulin resistance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction of insulin resistance is relative to the insulin resistance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, glucose tolerance is reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the reduction in glucose tolerance is relative to the glucose tolerance prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, glucose control is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in glucose control is relative to the glucose control prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, lipid levels reflecting dyslipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, lipid levels reflecting hyperlipidemia are reduced in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the reduction in lipid levels is relative to the lipid levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, bone mineral density is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone mineral density is relative to the bone mineral density prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, bone turnover is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in bone turnover is relative to the bone turnover prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fat mass is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in fat mass is relative to the fat mass prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, body weight is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in body weight is relative to the body weight prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, central obesity is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

wherein the decrease in central obesity is relative to the central obesity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, blood pressure is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in blood pressure is relative to the blood pressure prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the severity of hirsutism is decreased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the decrease in the severity of hirsutism is relative to the severity of hirsutism prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, menstrual cyclicity is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in menstrual cyclicity is relative to the menstrual cyclicity prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, control of testicular adrenal rest tumor is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in control of testicular adrenal rest tumor is relative to the control of testicular adrenal rest tumor prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, fertility is increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in fertility is relative to the fertility prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, gonadotropin levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in gonadotropin levels is relative to the gonadotropin levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, progesterone levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in progesterone levels is relative to the progesterone levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, semen levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in semen levels is relative to the semen levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, LH (luteinizing hormone) levels are increased in the subject after a time period of administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the increase in LH levels are relative to the LH levels prior to administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the time period of administration is at least about 4 weeks. In some embodiments, the time period of administration is at least about 24 weeks. In some embodiments, the time period of administration is at least about one year. In some embodiments, the time period of administration is at least 4 weeks. In some embodiments, the time period of administration is at least 24 weeks. In some embodiments, the time period of administration is at least one year. In some embodiments, the time period of administration is less than about 1 day. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6 or 7 days, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks, or within a range of any of the preceding values. In some embodiments, the time period of administration is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or within a range of any of the preceding values. It is understood that comparative measurements occur preferably during the morning.

In some embodiments, the subject is a pediatric subject. In some embodiments, the pediatric subject is less than or equal to six years old. In some embodiments, the pediatric subject is greater than six years old and less than eleven years old. In some embodiments, the pediatric subject is greater than ten years old and less than fifteen years old. In some embodiments, the pediatric subject is greater than fourteen years old and less than nineteen years old.

In some embodiments, the subject is an adult subject. In some embodiments, the subject is over eighteen years old. In some embodiments, the subject is female. In some embodiments, the subject is male.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described herein. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is

administered as a pharmaceutical composition described in Example 9. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 11. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 12. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition described in Example 13. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt described herein.

For the avoidance of doubt, also provided herein is the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, or corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

For the avoidance of doubt, also provided herein is use of the corresponding pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the corresponding methods, as described herein.

p-Toluenesulfonic Acid Salt

In some embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt thereof is 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

In some embodiments, the 4-(2-chloro-4-methoxy -5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt is a crystalline salt. In some embodiments, the p-toluenesulfonic acid crystalline salt has Form 1.

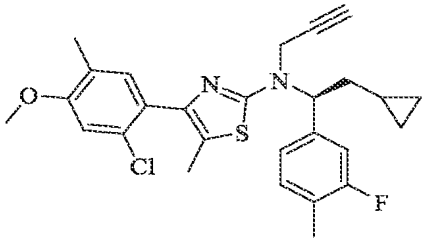
In some embodiments, the p-toluenesulfonic acid crystalline salt has an X-ray powder diffraction pattern as substantially shown in Figure 27. In some embodiments, the p-toluenesulfonic acid crystalline salt has a DSC thermogram substantially as depicted in Figure 28. In some embodiments, the p-toluenesulfonic acid crystalline salt has a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

In some embodiments, the p-toluenesulfonic acid crystalline salt has at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees. In some embodiments, the p-toluenesulfonic acid crystalline salt has an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

Lipidic Semi-Solid Formulation

Provided herein is a lipidic semi-solid formulation, which is a pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

In some embodiments, the pharmaceutical composition comprises an oily phase vehicle. An oily phase vehicle is a solvent that is poorly miscible with water. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 20 wt% to about 50 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35 wt% to about 45 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 39 wt% of the oily phase vehicle. In some embodiments, the pharmaceutical composition comprises about 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, or 45 wt% of the oily phase vehicle, or within a range of any of the preceding values.

In some embodiments, the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the oily phase vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides are Labrafac TM Lipophile WL1349. In some embodiments, the medium-chain triglycerides are Miglyol 812N.

In some embodiments, the pharmaceutical composition comprises an emulsifying agent. An emulsifying agent is a compound or substance that acts as a stabilizer for emulsions. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises

about 20 wt% of the emulsifying agent. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the emulsifying agent, or within a range of any of the preceding values.

In some embodiments, the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the emulsifying agent is propylene glycol dicaprylate/dicaprate. In some embodiments, the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

In some embodiments, the pharmaceutical composition comprises a nonionic surfactant. A nonionic surfactant is a substance with a hydrophilic head and a hydrophobic tail that has no charge that is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 50 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10 wt% to about 30 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 15 wt% to about 25 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 19 wt% of the nonionic surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 wt% of the nonionic surfactant, or within a range of any of the preceding values.

In some embodiments, the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides. In some embodiments, the nonionic surfactant is lauroyl polyoxyl-32 glycerides. In some embodiments, the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

In some embodiments, the pharmaceutical composition comprises a solubilizing agent. A solubilizing agent is a solvent that assists with solubilizing the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 50 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1 wt% to about 20 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 5 wt% to about 15 wt% of the solubilizing agent. In some

embodiments, the pharmaceutical composition comprises about 11 wt% of the solubilizing agent. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% of the solubilizing agent, or within a range of any of the preceding values.

In some embodiments, the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer. In some embodiments, the solubilizing agent is vitamin E polyethylene glycol succinate. In some embodiments, the vitamin E polyethylene glycol succinate is Kolliphor® TPGS. In some embodiments, the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) an oily phase vehicle;

(c) an emulsifying agent;

(d) a nonionic surfactant; and

(e) a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 35 wt% to about 45 wt% of an oily phase vehicle;

(c) about 15 wt% to about 25 wt% of an emulsifying agent;

(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and

(e) about 5 wt% to about 15 wt% of a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 39 wt% of an oily phase vehicle;

(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and

(e) about 11 wt% of a solubilizing agent.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) a medium-chain triglycerides component;

(c) a propylene glycol dicaprylate/dicaprate component;

(d) a lauroyl polyoxyl-32 glycerides component; and

(e) a vitamin E polyethylene glycol succinate component.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;

(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

In some embodiments, the pharmaceutical composition comprises:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 39 wt% of medium-chain triglycerides;

(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 11 wt% of vitamin E polyethylene glycol succinate.

In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 15 to about 40 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 26 to about 30 centipoise at about 45 °C. In some embodiments, the lipidic semi-solid pharmaceutical

composition has a viscosity between about 5 to about 25 centipoise at about 60 °C. In some embodiments, the lipidic semi-solid pharmaceutical composition has a viscosity between about 14 to about 18 centipoise at about 60 °C.

In some embodiments, the pharmaceutical composition does not comprise a combination of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

In some embodiments, the pharmaceutical composition does not comprise at least one of mannitol, croscarmellose sodium, maize starch, hydroxypropyl methylcellulose, and magnesium stearate.

In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in crystalline form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I), or pharmaceutically acceptable salt thereof, in amorphous form. In some embodiments, the pharmaceutical composition comprises a compound of Formula (I) as a free base. In some embodiments, the crystalline form of the compound of Formula (I) is of Form I.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg to about 150 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 25 mg, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film. In some embodiments, the pharmaceutical composition is in tablet form. In some embodiments, the pharmaceutical composition is in capsule form. In some embodiments, the dosage form is coated.

Some embodiments provide a method for preparing the pharmaceutical composition, comprising:

(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;

(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

In some embodiments, the method further comprises:

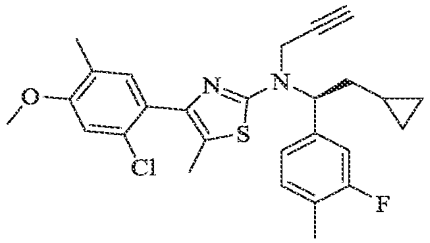
(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and

(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

Liquid Formulations

Provided herein is a pharmaceutical composition in oral solution dosage form comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free

base. In some embodiments, the pharmaceutical composition comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or within a range of any of the preceding values.

In some embodiments, the pharmaceutical composition comprises a sweetener. A sweetener is a formulation component added to improve taste. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.15 w/v% of the sweetener. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the sweetener, or within a range of any of the preceding values.

In some embodiments, the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame. In some embodiments, the sweetener is saccharin.

In some embodiments, the pharmaceutical composition comprises an anti-oxidant. An anti-oxidant is a formulation component included to improve stability by preventing oxidation. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.17 w/v% of the anti-oxidant. In some embodiments, the pharmaceutical composition comprises about 0.1, 0.2, 0.3, 0.4, or 0.5 w/v% of the anti-oxidant, or within a range of any of the preceding values.

In some embodiments, the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid. In some embodiments, the anti-oxidant is butylated hydroxytoluene.

In some embodiments, the pharmaceutical composition comprises a flavor. A flavor is a formulation component added to mask taste through aromatics. In some embodiments, the pharmaceutical composition comprises about 0.01 w/v% to about 0.5 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05 w/v% to about 0.2 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.10 w/v% of the flavor. In some embodiments, the pharmaceutical composition comprises about 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19 or 0.2 w/v% of the flavor, or within a range of any of the preceding values.

In some embodiments, the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor. In some embodiments, the flavor is FONA orange flavor.

A liquid vehicle is a solvent capable of dissolving or partially dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the purposes of delivery as an oral dosing solution. In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 99.9 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90 w/v% to about 99 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 92 w/v% to about 97 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 94.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 w/v% of the liquid vehicle, or within a range of any of the preceding values.

In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

In some embodiments, the pharmaceutical composition further comprises a surfactant. A surfactant is a formulation component added to improve solubility or emulsion properties. In some embodiments, the pharmaceutical composition comprises about 1 w/v% to about 50 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10 w/v% to about 30 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 20 w/v% of the surfactant. In some embodiments, the pharmaceutical composition comprises about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 w/v% of the surfactant, or within a range of any of the preceding values.

In some embodiments, the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters. In some

embodiments, the surfactant is oleoyl polyoxyl-6 glycerides. In some embodiments, the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

In some embodiments, the pharmaceutical composition comprises about 50 w/v% to about 90 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70 w/v% to about 80 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 75 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 74.6 w/v% of the liquid vehicle. In some embodiments, the pharmaceutical composition comprises about 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 w/v% of the liquid vehicle, or within a range of any of the preceding values.

In some embodiments, the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol. In some embodiments, the liquid vehicle is medium-chain triglycerides. In some embodiments, the medium-chain triglycerides is Labrafac Lipophile WL1349.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) a sweetener;

(c) an anti-oxidant;

(d) a flavor; and

(e) a liquid vehicle.

In some embodiments, the pharmaceutical composition further comprises a surfactant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and

(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;

(e) about 15 w/v% to about 25 w/v% of a surfactant; and

(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor;

(e) about 20 w/v% of a surfactant; and

(f) about 75 w/v% of a liquid vehicle.

In some embodiments, the pharmaceutical composition comprises:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) saccharin;

(c) butylated hydroxytoluene;

(d) FONA orange flavor; and

(e) medium-chain triglycerides.

In some embodiments, the pharmaceutical composition further comprises oleoyl polyoxyl-6 glycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor; and

(e) about 94.6 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;

(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor;

(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 75 w/v% of medium-chain triglycerides.

In some embodiments, the pharmaceutical composition comprises the compound of Formula (I) as a free base.

In some embodiments, the pharmaceutical composition is formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 50 mg/mL, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the unit dosage form in an amount of about 100 mg/mL, based on the weight of the free base.

In some embodiments, the liquid pharmaceutical composition has a viscosity between about 1 to about 50 centipoise at about 25 °C.

Some embodiments provide a method for preparing a pharmaceutical composition comprising:

(a) mixing a liquid vehicle with a sweetener;

(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and

(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

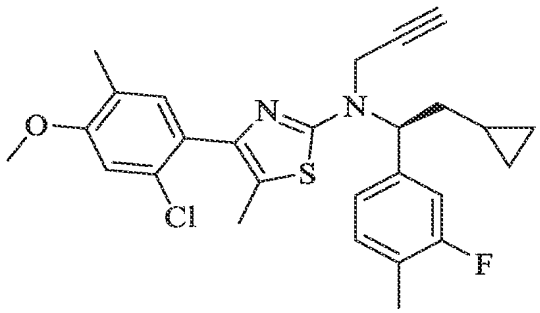
In some embodiments, step (a) of the method comprises mixing a liquid vehicle with a sweetener and a surfactant.

Spray-dried dispersions

The methods and uses of the present disclosure may comprise administering a spray-dried dispersion (SDDs) of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, and to the use of the SDDs in the treatment of congenital adrenal hyperplasia (CAH).

In some embodiments, concentration and bioavailability enhancement in an aqueous environment of a low-solubility drug in a spray-dried dispersion is achieved if the SDD exhibits one or more properties, including, for example: (1) the solid dispersion is substantially homogeneous; (2) the drug is substantially amorphous; (3) the SDD has a relatively high drug loading; and (4) the SDD has a low residual solvent content. In some embodiments, the dispersion, when administered to an aqueous environment, provides at least a temporary dissolved drug concentration in the aqueous environment that is greater than the solubility of the crystalline form of the drug in the same environment. The aqueous environment can be, for example, an *in vitro* environment, such as a dissolution test media (e.g., phosphate buffered saline (PBS) solution), or an *in vivo* environment, such as the gastrointestinal (GI) tract of an animal, for example, a human. In some embodiments, the aqueous environment is the lower GI tract, such as the small intestine and large intestine.

Provided in the present disclosure is a spray-dried dispersion that contains a polymer and a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof. In some embodiments, the SDD includes a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9.

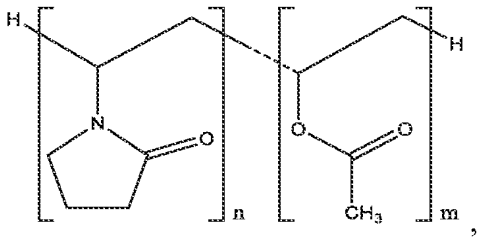
In some embodiments, the polymer is a neutral polymer. For example, the polymer does not contain any charged functional groups. In some embodiments, the neutral polymer is a cellulosic polymer. For example, the cellulosic polymer can be a polymer with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. Examples of suitable neutral polymers include, but are not limited to, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

In some embodiments, the polymer is an enteric polymer. An "enteric polymer," as used herein, is a polymeric substance that is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH of less than about 7 and which is substantially soluble or can decompose under conditions exhibiting a pH of about 7 or more. Examples of suitable enteric polymers include, but are not limited to, carboxymethyl ethyl cellulose (CMEC), cellulose acetate phthalate (CAP), cellulose acetate succinate (CAS), methylcellulose phthalate, hydroxymethyl ethyl cellulose phthalate, hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinyl alcohol phthalate, polyvinyl butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride, a copolymer of vinylbutylether/maleic anhydride, a copolymer of styrene/maleic acid monoester, a copolymer of methyl acrylate/methacrylic acid, a copolymer of styrene/acrylic acid, a copolymer of methyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate, an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, a methacrylic copolymer, and mixtures thereof. In some embodiments, the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl

cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer. In some embodiments, the enteric polymer is a Eudragit® polymer sold by Evonik Industries (Essen, Germany). In some embodiments, the enteric polymer is an amino methacrylate copolymer. In some embodiments, the amino methacrylate copolymer is Eudragit® E PO/100. In some embodiments, the enteric polymer is an ammonioalkyl methacrylate copolymer. In some embodiments, the ammonioalkyl methacrylate copolymer is Eudragit® RLPO. In some embodiments, the enteric polymer is a methacrylic copolymer. In some embodiments, the methacrylic copolymer is Eudragit® L100 or Eudragit® S100.

In some embodiments, the polymer is a pyrrolidone polymer. For example, the pyrrolidone polymer can be a vinyl pyrrolidone polymer, such as polyvinyl pyrrolidone (PVP) or polyvinyl pyrrolidone vinyl acetate (PVP/VA), including homopolymers and copolymers of PVP and homopolymers and copolymers of N-vinyl pyrrolidone. In some embodiments, the pyrrolidone polymer is PVP/VA. In some embodiments, the PVP/VA is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70 to about 70:30 by weight, such as about 40:60 to about 60:40 by weight, or about 45:55 to about 55:45 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 30:70, about 35:65, about 40:60, about 45:55, about 50:50, about 55:45, about 60:40, about 65:35, or about 70:30 by weight. In some embodiments, the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

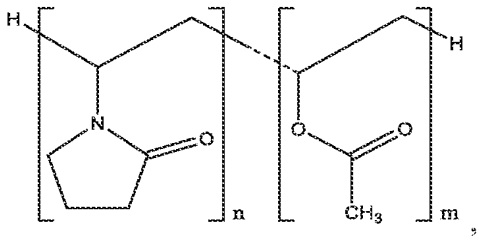
In some embodiments, the pyrrolidone polymer has the structure:



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where the value of n is about 1 to about 2 times the value of m. For example, the value of n can be about 1, about 1.05, about 1.1, about 1.15, about 1.16, about 1.2, about 1.25, about 1.3, about 1.35, about 1.4, about 1.45, about 1.5, about 1.55, about 1.6, about 1.65, about 1.7, about 1.75, about 1.8, about 1.85, about 1.9, about 1.95, or about 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is about 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is about 1.16 times the value of m.

In some embodiments, the pyrrolidone polymer has the structure:



where the value of n is 1 to 2 times the value of m. For example, the value of n can be 1, 1.05, 1.1, 1.15, 1.16, 1.2, 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, or 2 times the value of m, or a value within a range defined by any of the preceding values. In some embodiments, the value of n is 1.16 times the value of m. In some embodiments, the copolymer is copovidone, and the value of n is 1.16 times the value of m.

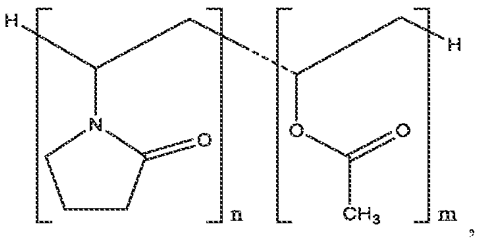
In some embodiments, the polymer used in the disclosed SDDs is present in an amount sufficient to increase the maximum drug concentration of the amorphous form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the environment of use (e.g., aqueous environment) relative to a control composition that contains an equivalent amount of a crystalline form of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, but without polymer. In some embodiments, once the SDD is introduced into an environment of use (e.g., aqueous environment), the polymer increases the aqueous concentration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, relative to the control composition. It is to be understood that the control composition is free from solubilizers or other components that would materially affect the solubility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is in solid form in the control composition.

In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from about 1:1 to about 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be about 1:1 to about 1:8, about 1:1 to about 1:7, about 1:1 to about 1:6, about 1:1 to about 1:5, about 1:1 to about 1:4, about 1:1 to about 1:3, about 1:1 to about 1:2, about 1:1 to about 1:1.5, about 1:1.5 to about 1:9, or about 1:2.5 to about 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9, about 1:8, about 1:7.5, about 1:7, about 1:6, about 1:5, about 1:4, about 1:3, about 1:2.5, about 1:2, about 1:1.5, or about 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight

ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is about 1:1.

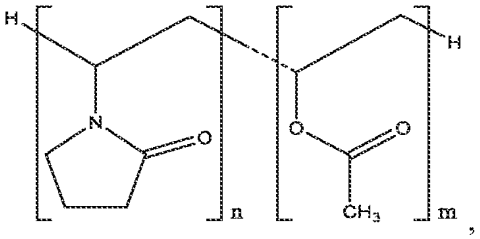
In some embodiments of the SDDs, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is from 1:1 to 1:9. For example, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer can be 1:1 to 1:8, 1:1 to 1:7, 1:1 to 1:6, 1:1 to 1:5, 1:1 to 1:4, 1:1 to 1:3, 1:1 to 1:2, 1:1 to 1:1.5, 1:1.5 to 1:9, or 1:2.5 to 1:4. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9, 1:8, 1:7.5, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2.5, 1:2, 1:1.5, or 1:1, or a weight ratio within a range defined by any of the preceding values. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:9. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.5. In some embodiments, the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the polymer is 1:1.

In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is about 1 to about 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from about 1:1 to about 1:9.

In some embodiments, the spray dried dispersion includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



where the value of n is 1 to 2 times the value of m and the copolymer contains 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of 60:40 by weight, and the weight ratio of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, to the copolymer is from 1:1 to 1:9.

In some embodiments of the SDDs, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer together form homogeneous particles. In some embodiments, the particles are a substantially homogeneous composition that includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer. As used herein, "substantially homogeneous" means that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, dispersed in the polymer. While the dispersion can have some concentrated domains of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, the dispersion itself has a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous particles of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and pure amorphous polymer particles, which generally displays two distinct T_gs, one of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one of the polymer. "T_g," as used herein, is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state.

In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of about 5 μm to about 100 μm, such as about 5 μm to about 95 μm, about 5 μm to about 90 μm, about 5 μm to about 85 μm, about 5 μm to about 80 μm, about 5 μm to about 75 μm, about 5 μm to about 70 μm, about 5 μm to about 65 μm, about 5 μm to about 60 μm, about 5 μm to about 55 μm, about 5 μm to about 50 μm, about 5 μm to about 45 μm, about 5 μm to about 40 μm, about 5 μm to about 35 μm, about 5 μm to about 30 μm, about 5 μm to about 25 μm, about 5 μm to about 20 μm, about 5 μm to about 15 μm, about 5 μm to about 10 μm, about 10 μm to about 100 μm, about 10 μm to about 95 μm, about 10 μm to about 90 μm, about 10 μm to

about 85 μm, about 10 μm to about 80 μm, about 10 μm to about 75 μm, about 10 μm to about 70 μm, about 10 μm to about 65 μm, about 10 μm to about 60 μm, about 10 μm to about 55 μm, about 10 μm to about 50 μm, about 10 μm to about 45 μm, about 10 μm to about 40 μm, about 10 μm to about 35 μm, about 10 μm to about 30 μm, about 10 μm to about 25 μm, about 10 μm to about 20 μm, about 10 μm to about 15 μm, about 15 μm to about 100 μm, about 15 μm to about 95 μm, about 15 μm to about 90 μm, about 15 μm to about 85 μm, about 15 μm to about 80 μm, about 15 μm to about 75 μm, about 15 μm to about 70 μm, about 15 μm to about 65 μm, about 15 μm to about 60 μm, about 15 μm to about 55 μm, about 15 μm to about 50 μm, about 15 μm to about 45 μm, about 15 μm to about 40 μm, about 15 μm to about 35 μm, about 15 μm to about 30 μm, about 15 μm to about 25 μm, about 15 μm to about 20 μm, about 20 μm to about 100 μm, about 20 μm to about 95 μm, about 20 μm to about 90 μm, about 20 μm to about 85 μm, about 20 μm to about 80 μm, about 20 μm to about 75 μm, about 20 μm to about 70 μm, about 20 μm to about 65 μm, about 20 μm to about 60 μm, about 20 μm to about 55 μm, about 20 μm to about 50 μm, about 20 μm to about 45 μm, about 20 μm to about 40 μm, about 20 μm to about 35 μm, about 20 μm to about 30 μm, about 20 μm to about 25 μm, about 25 μm to about 100 μm, about 25 μm to about 95 μm, about 25 μm to about 90 μm, about 25 μm to about 85 μm, about 25 μm to about 80 μm, about 25 μm to about 75 μm, about 25 μm to about 70 μm, about 25 μm to about 65 μm, about 25 μm to about 60 μm, about 25 μm to about 55 μm, about 25 μm to about 50 μm, about 25 μm to about 45 μm, about 25 μm to about 40 μm, about 25 μm to about 35 μm, about 25 μm to about 30 μm, about 30 μm to about 100 μm, about 30 μm to about 95 μm, about 30 μm to about 90 μm, about 30 μm to about 85 μm, about 30 μm to about 80 μm, about 30 μm to about 75 μm, about 30 μm to about 70 μm, about 30 μm to about 65 μm, about 30 μm to about 60 μm, about 30 μm to about 55 μm, about 30 μm to about 50 μm, about 30 μm to about 45 μm, about 30 μm to about 40 μm, about 30 μm to about 35 μm, about 35 μm to about 100 μm, about 35 μm to about 95 μm, about 35 μm to about 90 μm, about 35 μm to about 85 μm, about 35 μm to about 80 μm, about 35 μm to about 75 μm, about 35 μm to about 70 μm, about 35 μm to about 65 μm, about 35 μm to about 60 μm, about 35 μm to about 55 μm, about 35 μm to about 50 μm, about 35 μm to about 45 μm, about 35 μm to about 40 μm, about 40 μm to about 100 μm, about 40 μm to about 95 μm, about 40 μm to about 90 μm, about 40 μm to about 85 μm, about 40 μm to about 80 μm, about 40 μm to about 75 μm, about 40 μm to about 70 μm, about 40 μm to about 65 μm, about 40 μm to about 60 μm, about 40 μm to about 55 μm, about 40 μm to about 50 μm, about 40 μm to about 45 μm, about 45 μm to about 100 μm, about 45 μm to about 95 μm,

about 45 μm to about 90 μm, about 45 μm to about 85 μm, about 45 μm to about 80 μm, about 45 μm to about 75 μm, about 45 μm to about 70 μm, about 45 μm to about 65 μm, about 45 μm to about 60 μm, about 45 μm to about 55 μm, about 45 μm to about 50 μm, about 50 μm to about 100 μm, about 50 μm to about 95 μm, about 50 μm to about 90 μm, about 50 μm to about 85 μm, about 50 μm to about 80 μm, about 50 μm to about 75 μm, about 50 μm to about 70 μm, about 50 μm to about 65 μm, about 50 μm to about 60 μm, about 50 μm to about 55 μm, about 55 μm to about 100 μm, about 55 μm to about 95 μm, about 55 μm to about 90 μm, about 55 μm to about 85 μm, about 55 μm to about 80 μm, about 55 μm to about 75 μm, about 55 μm to about 70 μm, about 55 μm to about 65 μm, about 55 μm to about 60 μm, about 60 μm to about 100 μm, about 60 μm to about 95 μm, about 60 μm to about 90 μm, about 60 μm to about 85 μm, about 60 μm to about 80 μm, about 60 μm to about 75 μm, about 60 μm to about 70 μm, about 60 μm to about 65 μm, about 65 μm to about 100 μm, about 65 μm to about 95 μm, about 65 μm to about 90 μm, about 65 μm to about 85 μm, about 65 μm to about 80 μm, about 65 μm to about 75 μm, about 65 μm to about 70 μm, about 70 μm to about 100 μm, about 70 μm to about 95 μm, about 70 μm to about 90 μm, about 70 μm to about 85 μm, about 70 μm to about 80 μm, about 70 μm to about 75 μm, about 75 μm to about 100 μm, about 75 μm to about 95 μm, about 75 μm to about 90 μm, about 75 μm to about 85 μm, about 75 μm to about 80 μm, about 80 μm to about 100 μm, about 80 μm to about 95 μm, about 80 μm to about 90 μm, about 80 μm to about 85 μm, about 85 μm to about 100 μm, about 85 μm to about 95 μm, about 85 μm to about 90 μm, about 90 μm to about 100 μm, about 90 μm to about 95 μm, or about 95 μm to about 100 μm. In some embodiments, the D_{50} is about 5 μm, about 10 μm, about 15 μm, about 16 μm, about 20 μm, about 25 μm, about 30 μm, about 35 μm, about 40 μm, about 45 μm, about 50 μm, about 55 μm, about 60 μm, about 65 μm, about 70 μm, about 75 μm, about 80 μm, about 85 μm, about 90 μm, about 95 μm, or about 100 μm. In some embodiments, the D_{50} is about 10 μm, about 11 μm, about 12 μm, about 13 μm, about 14 μm, about 15 μm, about 16 μm, about 17 μm, about 18 μm, about 19 μm, or about 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is about 16 μm. The D_{50} value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

In some embodiments, the particles have a particle size distribution (D-value, D_{50}), of 5 μm to 100 μm, such as 5 μm to 95 μm, 5 μm to 90 μm, 5 μm to 85 μm, 5 μm to 80 μm, 5

μm to 75 μm, 5 μm to 70 μm, 5 μm to 65 μm, 5 μm to 60 μm, 5 μm to 55 μm, 5 μm to 50 μm, 5 μm to 45 μm, 5 μm to 40 μm, 5 μm to 35 μm, 5 μm to 30 μm, 5 μm to 25 μm, 5 μm to 20 μm, 5 μm to 15 μm, 5 μm to 10 μm, 10 μm to 100 μm, 10 μm to 95 μm, 10 μm to 90 μm, 10 μm to 85 μm, 10 μm to 80 μm, 10 μm to 75 μm, 10 μm to 70 μm, 10 μm to 65 μm, 10 μm to 60 μm, 10 μm to 55 μm, 10 μm to 50 μm, 10 μm to 45 μm, 10 μm to 40 μm, 10 μm to 35 μm, 10 μm to 30 μm, 10 μm to 25 μm, 10 μm to 20 μm, 10 μm to 15 μm, 15 μm to 100 μm, 15 μm to 95 μm, 15 μm to 90 μm, 15 μm to 85 μm, 15 μm to 80 μm, 15 μm to 75 μm, 15 μm to 70 μm, 15 μm to 65 μm, 15 μm to 60 μm, 15 μm to 55 μm, 15 μm to 50 μm, 15 μm to 45 μm, 15 μm to 40 μm, 15 μm to 35 μm, 15 μm to 30 μm, 15 μm to 25 μm, 15 μm to 20 μm, 20 μm to 100 μm, 20 μm to 95 μm, 20 μm to 90 μm, 20 μm to 85 μm, 20 μm to 80 μm, 20 μm to 75 μm, 20 μm to 70 μm, 20 μm to 65 μm, 20 μm to 60 μm, 20 μm to 55 μm, 20 μm to 50 μm, 20 μm to 45 μm, 20 μm to 40 μm, 20 μm to 35 μm, 20 μm to 30 μm, 20 μm to 25 μm, 25 μm to 100 μm, 25 μm to 95 μm, 25 μm to 90 μm, 25 μm to 85 μm, 25 μm to 80 μm, 25 μm to 75 μm, 25 μm to 70 μm, 25 μm to 65 μm, 25 μm to 60 μm, 25 μm to 55 μm, 25 μm to 50 μm, 25 μm to 45 μm, 25 μm to 40 μm, 25 μm to 35 μm, 25 μm to 30 μm, 30 μm to 100 μm, 30 μm to 95 μm, 30 μm to 90 μm, 30 μm to 85 μm, 30 μm to 80 μm, 30 μm to 75 μm, 30 μm to 70 μm, 30 μm to 65 μm, 30 μm to 60 μm, 30 μm to 55 μm, 30 μm to 50 μm, 30 μm to 45 μm, 30 μm to 40 μm, 30 μm to 35 μm, 35 μm to 100 μm, 35 μm to 95 μm, 35 μm to 90 μm, 35 μm to 85 μm, 35 μm to 80 μm, 35 μm to 75 μm, 35 μm to 70 μm, 35 μm to 65 μm, 35 μm to 60 μm, 35 μm to 55 μm, 35 μm to 50 μm, 35 μm to 45 μm, 35 μm to 40 μm, 40 μm to 100 μm, 40 μm to 95 μm, 40 μm to 90 μm, 40 μm to 85 μm, 40 μm to 80 μm, 40 μm to 75 μm, 40 μm to 70 μm, 40 μm to 65 μm, 40 μm to 60 μm, 40 μm to 55 μm, 40 μm to 50 μm, 40 μm to 45 μm, 45 μm to 100 μm, 45 μm to 95 μm, 45 μm to 90 μm, 45 μm to 85 μm, 45 μm to 80 μm, 45 μm to 75 μm, 45 μm to 70 μm, 45 μm to 65 μm, 45 μm to 60 μm, 45 μm to 55 μm, 45 μm to 50 μm, 50 μm to 100 μm, 50 μm to 95 μm, 50 μm to 90 μm, 50 μm to 85 μm, 50 μm to 80 μm, 50 μm to 75 μm, 50 μm to 70 μm, 50 μm to 65 μm, 50 μm to 60 μm, 50 μm to 55 μm, 55 μm to 100 μm, 55 μm to 95 μm, 55 μm to 90 μm, 55 μm to 85 μm, 55 μm to 80 μm, 55 μm to 75 μm, 55 μm to 70 μm, 55 μm to 65 μm, 55 μm to 60 μm, 60 μm to 100 μm, 60 μm to 95 μm, 60 μm to 90 μm, 60 μm to 85 μm, 60 μm to 80 μm, 60 μm to 75 μm, 60 μm to 70 μm, 60 μm to 65 μm, 65 μm to 100 μm, 65 μm to 95 μm, 65 μm to 90 μm, 65 μm to 85 μm, 65 μm to 80 μm, 65 μm to 75 μm, 65 μm to 70 μm, 70 μm to 100 μm, 70 μm to 95 μm, 70 μm to 90 μm, 70 μm to 85 μm, 70 μm to 80 μm, 70 μm to 75 μm, 75 μm to 100 μm, 75 μm to 95 μm, 75 μm to 90 μm, 75 μm to 85 μm, 75 μm to 80 μm, 80 μm to 100 μm, 80 μm to 95 μm, 80 μm to 90 μm, 80 μm

to 85 μm, 85 μm to 100 μm, 85 μm to 95 μm, 85 μm to 90 μm, 90 μm to 100 μm, 90 μm to 95 μm, or 95 μm to 100 μm. In some embodiments, the D_{50} is 5 μm, 10 μm, 15 μm, 16 μm, 20 μm, 25 μm, 30 μm, 35 μm, 40 μm, 45 μm, 50 μm, 55 μm, 60 μm, 65 μm, 70 μm, 75 μm, 80 μm, 85 μm, 90 μm, 95 μm, or 100 μm. In some embodiments, the D_{50} is 10 μm, 11 μm, 12 μm, 13 μm, 14 μm, 15 μm, 16 μm, 17 μm, 18 μm, 19 μm, or 20 μm, or a value within a range defined by any of the preceding values. In some embodiments, the D_{50} value is 16 μm. The D_{50} value can be measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, laser diffraction and disc centrifugation.

The SDDs of the present disclosure have a low residual solvent content. "Residual solvent content," as used herein, refers to the amount of solvent present in the SDD following spray drying, immediately upon exit from the spray dryer. The presence of solvent in the SDD lowers the glass transition temperature (T_g) of the dispersion. In some embodiments, mobility of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the SDD and its propensity to phase separate and crystallize decreases as the amount of residual solvent in the SDD decreases. In some embodiments, the SDDs have a residual solvent content of not more than about 10 wt%, such as not more than about 5 wt%, or not more than about 1 wt%. For example, the SDDs have a residual solvent content of about 2 wt%, about 1.9 wt%, about 1.8 wt%, about 1.7 wt%, about 1.6 wt%, about 1.5 wt%, about 1.4 wt%, about 1.3 wt%, about 1.2 wt%, about 1.1 wt%, about 1 wt%, about 0.9 wt%, about 0.8 wt%, about 0.7 wt%, about 0.6 wt%, about 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than about 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than about 1 wt%. In some embodiments, the SDDs have a residual solvent content of about 0.5 wt% or less. In some embodiments, the SDDs have a residual solvent content of not more than 10 wt%, such as not more than 5 wt%, or not more than 1 wt%. For example, the SDDs may have a residual solvent content of 2 wt%, 1.9 wt%, 1.8 wt%, 1.7 wt%, 1.6 wt%, 1.5 wt%, 1.4 wt%, 1.3 wt%, 1.2 wt%, 1.1 wt%, 1 wt%, 0.9 wt%, 0.8 wt%, 0.7 wt%, 0.6 wt%, 0.5 wt%, or less. In some embodiments, the SDDs have a residual solvent content of less than 2 wt%. In some embodiments, the SDDs have a residual solvent content of less than 1 wt%. In some embodiments, the SDDs have a residual solvent content of 0.5 wt% or less.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the spray-dried dispersion is substantially amorphous. As used herein,

"substantially amorphous" means that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in amorphous form is at least 60 wt% and that the amount of crystalline form present does not exceed 20 wt%. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the dispersion is "almost completely amorphous," meaning that at least 90 wt% of the drug is amorphous, or that the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the crystalline form does not exceed 10 wt%. Amounts of crystalline drug can be measured by powder X-ray diffraction (PXRD), scanning electron microscope (SEM) analysis, differential scanning calorimetry (DSC), polarized light microscopy (PLM), or any other standard quantitative or qualitative measurement used to detect crystalline material. Without wishing to be bound by any theory, it is believed that the amorphous, or non-crystalline form, in combination with the polymer, leads to greater ease of dissolution and absorption in the desired location, for example, the intestines, resulting in enhanced bioavailability as compared to a crystalline form of the compound of Formula (I) without polymer.

Process for preparing spray-dried dispersions

Provided in the present disclosure are methods for preparing a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as the SDDs described herein. In some embodiments, the method includes dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer. In some embodiments, the product obtained by spray-drying is dried to remove the solvent or solvent mixture. In some embodiments, the organic solvent is acetone.

The SDDs disclosed herein can be obtained by spray-drying a mixture comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more polymer(s), and an appropriate solvent or solvent mixture. Spray-drying involves atomization of a liquid mixture containing, for example, a solid and a solvent or solvent mixture, and removal of the solvent or solvent mixture. Atomization can be done, for example, through a two-fluid or pressure or electrosonic nozzle, or on a rotating disk.

Spray-drying converts a liquid feed to a dried particulate form. In some embodiments, spray-drying involves the atomization of a liquid feed solution into a spray of droplets and

contacting the droplets with hot air or gas in a drying chamber. The composition to be spray-dried can be any solution, coarse suspension, slurry, colloidal dispersion, or paste that can be atomized using the selected spray-drying apparatus. In some embodiments, the composition is a solution that is clear and free of undissolved solids. In some embodiments, the sprays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Commercially available types of apparatus can be used to conduct the spray-drying. For example, commercial spray dryers are manufactured by Buchi Ltd. and Niro (e.g., the PSD line of spray driers manufactured by Niro). Techniques and methods for spray-drying can also be found in *Perry's Chemical Engineering Handbook*, 6th Ed., R. H. Perry, D. W. Green & J. O. Maloney, eds., McGraw-Hill Book Co. (1984); and Marshall, "Atomization and Spray-Drying" 50, Chem. Eng. Prog. Monogr. Series 2 (1954).

In some embodiments, the spray-drying is conducted with an inlet temperature of from about 40°C to about 100°C, for example, from about 60°C to about 80°C, or from about 70°C to about 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 70°C, about 72°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, or about 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 60°C to about 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of about 61°C, about 63°C, about 65°C, about 67°C, about 69°C, about 71°C, about 73°C, about 75°C, about 77°C, about 79°C, about 81°C, about 83°C, or about 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is about 72°C.

In some embodiments, the spray-drying is conducted with an inlet temperature of from 40°C to 100°C, for example, from 60°C to 80°C, or from 70°C to 75°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 40°C, 45°C, 50°C, 55°C, 60°C, 70°C, 72°C, 75°C, 80°C, 85°C, 90°C, 95°C, or 100°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 60°C to 80°C. In some embodiments, the spray-drying is conducted with an inlet temperature of 61°C, 63°C, 65°C, 67°C, 69°C, 71°C, 73°C, 75°C, 77°C, 79°C, 81°C, 83°C, or 85°C, or within a range defined by any of the preceding values. In some embodiments, the inlet temperature is 72°C.

In some embodiments, the spray-drying is conducted with an outlet temperature of from about 20°C to about 75°C, for example, from about 25°C to about 50°C, or from about 30°C

to about 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 20°C, about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, or about 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 25°C to about 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of about 24°C, about 26°C, about 28°C, about 30°C, about 32°C, about 34°C, about 36°C, about 38°C, about 40°C, about 42°C, about 44°C, or about 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is about 35°C.

In some embodiments, the spray-drying is conducted with an outlet temperature of from 20°C to 75°C, for example, from 25°C to 50°C, or from 30°C to 40°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 20°C, 25°C, 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, or 75°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 25°C to 45°C. In some embodiments, the spray-drying is conducted with an outlet temperature of 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, or 46°C, or within a range defined by any of the preceding values. In some embodiments, the outlet temperature is 35°C.

In some embodiments, the method involves removing the organic solvent after formation of the spray-dried dispersion. In some embodiments, the organic solvent is removed by drying the SDD. In some embodiments, a secondary drying process, such as fluidized bed drying, vacuum drying, tray drying, microwave drying, rotary drum drying or biconical vacuum drying is used to remove or reduce residual solvents, such as the organic solvent, to pharmaceutically acceptable levels. In some embodiments, the SDD is dried with a convection tray dryer.

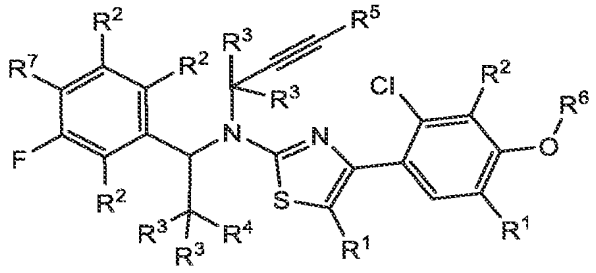
In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than about 0.2 g/mL, or less than about 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of about 0.19 g/mL, about 0.18 g/mL, about 0.17 g/mL, about 0.16 g/mL, about 0.15 g/mL, about 0.14 g/mL, about 0.13 g/mL, about 0.12 g/mL, about 0.11 g/mL, about 0.1 g/mL, about 0.09 g/mL, about 0.08 g/mL, about 0.07 g/mL, about 0.06 g/mL or about 0.05 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density of less than 0.2 g/mL, or less than 0.15 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a bulk density

of 0.19 g/mL, 0.18 g/mL, 0.17 g/mL, 0.16 g/mL, 0.15 g/mL, 0.14 g/mL, 0.13 g/mL, 0.12 g/mL, 0.11 g/mL, 0.1 g/mL, 0.09 g/mL, 0.08 g/mL, 0.07 g/mL, 0.06 g/mL or 0.05 g/mL, or within a range defined by any of the preceding values. The term "bulk density," as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than about 0.3 g/mL, or less than about 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of about 0.29 g/mL, about 0.28 g/mL, about 0.27 g/mL, about 0.26 g/mL, about 0.25 g/mL, about 0.24 g/mL, about 0.23 g/mL, about 0.22 g/mL, about 0.21 g/mL, about 0.2 g/mL, or about 0.19 g/mL, or within a range defined by any of the preceding values. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of less than 0.3 g/mL, or less than 0.25 g/mL. In some embodiments, the homogeneous particles produced by the methods of the present disclosure have a tapped density of 0.29 g/mL, 0.28 g/mL, 0.27 g/mL, 0.26 g/mL, 0.25 g/mL, 0.24 g/mL, 0.23 g/mL, 0.22 g/mL, 0.21 g/mL, 0.2 g/mL, or 0.19 g/mL, or within a range defined by any of the preceding values. The term "tap density" or "tapped density," as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

Deuterated Compounds

Also disclosed herein are compounds having the structure of the following formula (II):



(II)

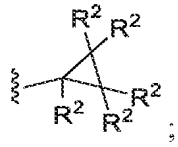
or a pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently $C(R^A)_3$;

each R^A is independently hydrogen or deuterium;

each R^2 is independently hydrogen or deuterium;

each R^3 is independently hydrogen or deuterium;

R^4 is  ;

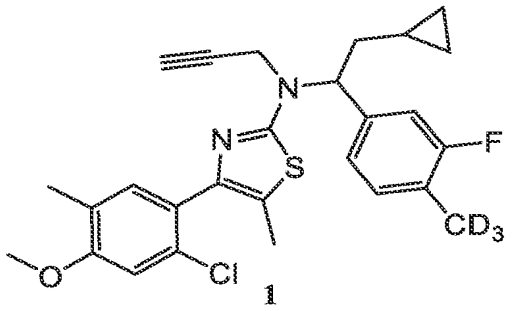
R^5 is hydrogen or deuterium;

R^6 is $C(R^A)_3$; and

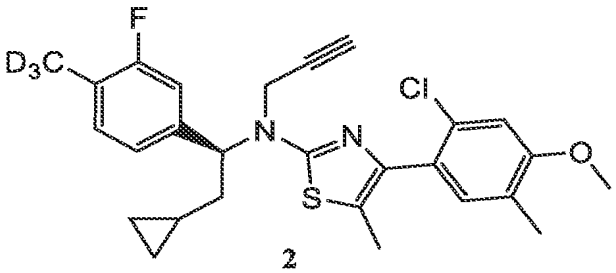
R^7 is $C(R^B)_3$, wherein at least one of R^A, R^B, R^2, R^3 and R^5 is deuterium.

With regard to the compounds provided herein, when a particular atomic position is designated as having deuterium or "D" or "d", it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of, in certain embodiments, at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation) at each designated deuterium position.

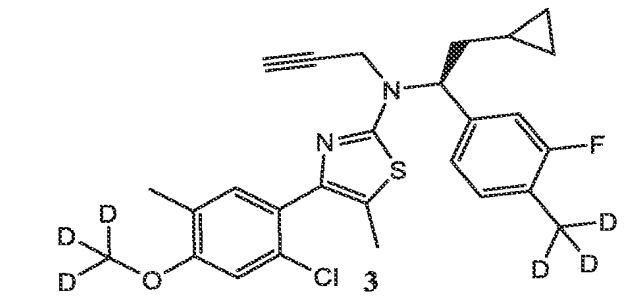
In some embodiments, the compound of Formula (II) may be one of the following, or a pharmaceutically acceptable salt thereof:



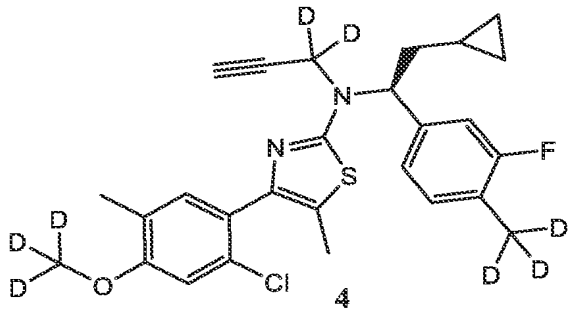
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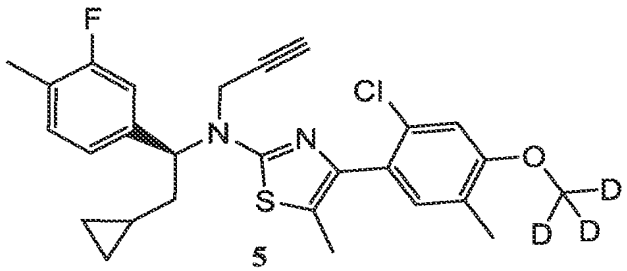
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Pharmaceutical compositions

The methods and uses disclosed herein can comprise administering the compound of Formula (I) as a pharmaceutical composition.

In some embodiments of the methods described herein, the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition further comprising one or more pharmaceutically acceptable excipients.

Also provided herein is a pharmaceutical composition comprising 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in any of the methods described herein.

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that does not comprise a spray-dried dispersion of the compound

of Formula (I), as specified, e.g., in Example 1. Accordingly, in some embodiments, the pharmaceutical composition does not comprise any of the following polymers: hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); HPMCAS-M; and methyl methacrylate copolymer (1:1) (Eudragit® L100).

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is not the reference formulation described in Example 9. Accordingly, in some embodiments, the pharmaceutical composition does not comprise at least three of the excipients selected from caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 9. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 11. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 12. In some embodiments, the methods and uses described herein comprise administering a pharmaceutical composition that is the formulation described in Example 13.

In some embodiments, the pharmaceutical compositions include a spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 20% to about 90% w/w of the composition, such as about 20% to about 85%, about 20% to about 80%, about 20% to about 75%, about 20% to about 70%, about 20% to about 65%, about 20% to about 60%, about 20% to about 55%, about 20% to about 50%, about 20% to about 45%, about 20% to about 40%, about 20% to about 35%, about 20% to about 30%, about 20%

to about 25%, about 25% to about 90%, about 25% to about 85%, about 25% to about 80%, about 25% to about 75%, about 25% to about 70%, about 25% to about 65%, about 25% to about 60%, about 25% to about 55%, about 25% to about 50%, about 25% to about 45%, about 25% to about 40%, about 25% to about 35%, about 25% to about 30%, about 30% to about 90%, about 30% to about 85%, about 30% to about 80%, about 30% to about 75%, about 30% to about 70%, about 30% to about 65%, about 30% to about 60%, about 30% to about 55%, about 30% to about 50%, about 30% to about 45%, about 30% to about 40%, about 30% to about 35%, about 35% to about 90%, about 35% to about 85%, about 35% to about 80%, about 35% to about 75%, about 35% to about 70%, about 35% to about 65%, about 35% to about 60%, about 35% to about 55%, about 35% to about 50%, about 35% to about 45%, about 35% to about 40%, about 40% to about 90%, about 40% to about 85%, about 40% to about 80%, about 40% to about 75%, about 40% to about 70%, about 40% to about 65%, about 40% to about 60%, about 40% to about 55%, about 40% to about 50%, about 40% to about 45%, about 45% to about 90%, about 45% to about 85%, about 45% to about 80%, about 45% to about 75%, about 45% to about 70%, about 45% to about 65%, about 45% to about 60%, about 45% to about 55%, about 45% to about 50%, about 50% to about 90%, about 50% to about 85%, about 50% to about 80%, about 50% to about 75%, about 50% to about 70%, about 50% to about 65%, about 50% to about 60%, about 50% to about 55%, about 55% to about 90%, about 55% to about 85%, about 55% to about 80%, about 55% to about 75%, about 55% to about 70%, about 55% to about 65%, about 55% to about 60%, about 60% to about 90%, about 60% to about 85%, about 60% to about 80%, about 60% to about 75%, about 60% to about 70%, about 60% to about 65%, about 65% to about 90%, about 65% to about 85%, about 65% to about 80%, about 65% to about 75%, about 65% to about 70%, about 70% to about 90%, about 70% to about 85%, about 70% to about 80%, about 70% to about 75%, about 75% to about 90%, about 75% to about 85%, about 75% to about 80%, about 80% to about 90%, about 80% to about 85%, or about 85% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 90% w/w of the composition. In some embodiments, the SDD is present in an amount of about 40% to about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 60% to about 80% w/w of the composition. In some embodiments, the SDD is present in an amount of about 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

In some embodiments, the pharmaceutical composition includes the SDD comprising a compound of Formula (I) and one or more pharmaceutically acceptable excipients. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 20% to 90% w/w of the composition, such as 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to about 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 90%, 80% to 85%, or about 85% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 90% w/w of the composition. In some embodiments, the SDD is present in an amount of 40% to 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of 60% to 80% w/w of the composition. In some embodiments, the SDD is present in an amount of 80% w/w of the composition. In some embodiments, the SDD is present in the pharmaceutical composition in an amount of about 1% to about 20% w/w of the composition, such as about 13% w/w of the composition.

In some embodiments of the pharmaceutical compositions disclosed herein (e.g., a composition including an SDD), the pharmaceutically acceptable excipient is selected from the group consisting of a filler, a lubricant, and combinations thereof. In some embodiments, the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

In some embodiments, the pharmaceutical composition includes a filler. In some embodiments, the filler is selected from among binders, diluents, disintegrants, glidants, surfactants, and combinations thereof.

In some embodiments, the filler include saccharides (e.g., sugars, starch, and cellulose), gelatin, calcium carbonate, and synthetic polymers (e.g., polyvinylpyrrolidone, polyethylene glycol, and poloxamers (e.g., Poloxamer 188, a copolymer of polyoxyethylene and polyoxypropylene)). Exemplary fillers include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (e.g., Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm) or Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a polymethacrylate, dibasic calcium phosphate, magnesium stearate, calcium stearate, sodium stearate, stearic acid, hydrogenated vegetable oils, a mineral oil, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, sodium acetate, aliginic acid, alginates (e.g., sodium alginate), calcium silicate, and ion exchange resins. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethylcellulose. Exemplary fillers include cross-linked polyvinylpyrrolidone such as with an average particle size of 90 μm to 130 μm) or with an average particle size of 10 μm to 30 μm). Other fillers known to those of skill in the art are also contemplated as being useful when formulated in the pharmaceutical compositions described herein.

In some embodiments, the filler is a binder. Binders include agents that hold the active pharmaceutical ingredient (e.g., spray-dried dispersion containing a polymer and the compound of Formula (I), or a pharmaceutically acceptable salt thereof) and inactive ingredients together in a cohesive mix. Exemplary binders include, but are not limited to, glucose, sucrose, lactose, a starch, including modified starches such as sodium starch glycolate (Explotab®), xylitol, dextrin, saccharose, sorbitol, mannitol (e.g., Parteck® M 200 (mannitol with an average particle size of about 50 μm to about 500 μm), Parteck® M 100 (mannitol with an average particle size of less than 212 μm)), gelatin, gum tragacanth, acacia mucilage, a cellulose, a polyvinylpyrrolidone, a polyethylene glycol, a polyvinyl alcohol, a

polymethacrylate, and sodium starch glycolate. Exemplary cellulose fillers include microcrystalline cellulose (e.g., Avicel® PH-101 (microcrystalline cellulose with an average particle size of approximately 50 μm) or Avicel® PH 200 (microcrystalline cellulose with an average particle size of approximately 180 μm)), cellulose ethers, methyl cellulose, ethyl cellulose, croscarmellose sodium, sodium carboxy methyl cellulose starches, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. Exemplary polyvinylpyrrolidone fillers include cross-linked polyvinylpyrrolidone such as Kollidon® CL (crospovidone with an average particle size of 90 μm to 130 μm) or Kollidon® CL-SF (crospovidone with an average particle size of 10 μm to 30 μm). Other binders known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the filler is a diluent. Suitable diluents include, but are not limited to, lactose, mannitol, isomalt, sucrose, dextrose, and sorbitol.

In some embodiments, the filler is a disintegrant. Disintegrants include any agent that promotes breakup of the formulation in an aqueous environment, for example, to promote more rapid release of the active pharmaceutical ingredient (e.g., the compound of Formula (I), or a pharmaceutically acceptable salt thereof). Exemplary disintegrants include, but are not limited to, starch and modified starches, such as corn starch, potato starch, sodium starch glycolate or croscarmellose sodium, alginic acid, alginates, such as sodium alginate, polyvinylpyrrolidone, bentonite, methylcellulose, agar, carboxymethylcellulose, crospovidone, acid-carbonate effervescent systems, such as citric acid with bicarbonate salts, and ion exchange resins. Other disintegrants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the pharmaceutical composition comprises a disintegrant. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 30 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 5 w/w% to about 15 w/w% of the disintegrant. In some embodiments, the pharmaceutical composition comprises about 10 w/w% of the disintegrant. In some embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate. In some embodiments, the disintegrant is croscarmellose sodium.

In some embodiments, the filler is a glidant. Glidants can be used to improve the flowability of a powder or granules or both. Glidants include, but are not limited to, silicone dioxide, such as colloidal silicon dioxide or hydrated silicon dioxide, magnesium silicate,

magnesium aluminometasilicate, talc, starch, calcium silicate, light anhydrous silicic acid, and silicon dioxide aerogels.

In some embodiments, the pharmaceutical composition comprises a glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 5 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the glidant. In some embodiments, the pharmaceutical composition comprises about 0.67 w/w% of the glidant. In some embodiments, the glidant is selected from calcium silicate, silicon dioxide, and talc. In some embodiments, the glidant is calcium silicate.

In some embodiments, the filler is a surfactant, wetting agent, solubilizer, or combination thereof. Examples include, but are not limited to, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., Tween®), polyoxyethylene stearates, sodium dodecylsulfate, tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton). Other examples include, but are not limited to, poloxamers such as Pluronic® F68, F127, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic® 908 (also known as Poloxamine® 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (available from BASF), dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol® OT, which is a dioctyl ester of sodium sulfosuccinic acid (available from American Cyanimid), Duponol® P, which is a sodium lauryl sulfate (available from DuPont), Triton® X-200, which is an alkyl aryl polyether sulfonate (available from Rohm and Haas), Tween® 20 and Tween® 80, which are polyoxyethylene sorbitan fatty acid esters (available from ICI Specialty Chemicals), Carbowax™ 3550 and 934, which are polyethylene glycols (available from Union Carbide), Crodesta™ F-110, which is a mixture of sucrose stearate and sucrose distearate, and Crodesta™ SL-40 (both available from Croda Inc.), and SA90HCO, which has the chemical formula $C_{18}H_{37}—CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$.

In some embodiments, the pharmaceutical composition comprises a filler. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 99 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 90 w/w% of the filler. In some embodiments, the pharmaceutical composition comprises about 75.5 w/w% of the filler. In some embodiments, the filler is selected from

mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof. In some embodiments, the filler is a combination of mannitol and microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 30 w/w% to about 80 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 50 w/w% to about 60 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol. In some embodiments, the pharmaceutical composition comprises about 1 w/w% to about 50 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 10 w/w% to about 30 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 20 w/w% of microcrystalline cellulose. In some embodiments, the pharmaceutical composition comprises about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

In some embodiments, the pharmaceutical composition includes a lubricant. Lubricants are agents added to pharmaceutical formulations to reduce friction during processing and prevent ingredients from clumping together. Exemplary lubricants include, but are not limited to, talc, starch, magnesium stearate, calcium stearate, sodium stearate, zinc stearate, stearic acid, vegetable stearin, adipic acid, waxy fatty acids, such as glyceryl behenate, a hydrogenated vegetable oil, a mineral oil, a polyethylene glycol, lycopodium, sodium lauryl sulfate, magnesium lauryl sulfate, glyceryl palmitostearate, sodium benzoate, sodium chloride, sterotex, glycerol monostearate, sodium stearyl fumarate, colloidal silicon dioxide, sodium benzoate, sodium oleate, and sodium acetate. Other lubricants known to those of skill in the art are also contemplated as being useful when formulated in the compositions described herein.

In some embodiments, the pharmaceutical composition comprises a lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 10 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.1 w/w% to about 1 w/w% of the lubricant. In some embodiments, the pharmaceutical composition comprises about 0.5 w/w% of the lubricant. In some embodiments, the pharmaceutical lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc. In some embodiments, the lubricant is sodium stearyl fumarate.

In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) a glidant;

(c) a filler; and

(d) a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.1 w/w% to about 1 w/w% of a glidant;

(c) about 50 w/w% to about 90 w/w% of a filler; and

(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a polymer;

(b) about 0.67 w/w% of a glidant;

(c) about 75.5 w/w% of a filler; and

(d) about 10 w/w% of a disintegrant.

In some embodiments, the pharmaceutical composition comprises:

(a) the spray-dried dispersion of Example 3;

(b) calcium silicate;

(c) a combination of mannitol and microcrystalline cellulose; and

(d) croscarmellose sodium.

In some embodiments, the pharmaceutical composition comprises:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;

(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and

(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

In some embodiments, the pharmaceutical composition comprises:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.67 w/w% of calcium silicate;

(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and

(d) about 10 w/w% of croscarmellose sodium.

Additional excipients can be included in the pharmaceutical formulations of the present disclosure. Further examples of excipients include, but are not limited to, pigments, colorants, flavoring agents, preservatives, and sweeteners. Flavors and colors can be added to improve the taste or appearance of a formulation. Examples of preservatives used in pharmaceutical compositions are aromatic alcohols, such as benzyl or phenol alcohol, antioxidants such as vitamin A, vitamin E, vitamin C, and selenium, amino acids such as cysteine and methionine, citric acid and sodium citrate, or synthetic preservatives such as methyl paraben and propyl paraben. Sweeteners can be added to make the ingredients more palatable, especially in chewable tablets or liquids like syrups.

Also provided are methods for preparing a pharmaceutical composition, such as a pharmaceutical composition of the present disclosure. In some embodiments, the method includes combining the spray-dried dispersion described herein with one or more pharmaceutically acceptable excipients, e.g., a pharmaceutically acceptable excipient described herein.

In some embodiments, the method for preparing the pharmaceutical composition comprises:

(a) blending the spray-dried dispersion described herein, with a glidant;

(b) further blending the blend of step (a) with a filler and a disintegrant;

(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;

(d) further blending the intragranular blend of step (c);

(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and

(f) milling of ribbon from roller compaction into granules of step (e).

In some embodiments, the spray-dried dispersion is the spray-dried dispersion described in Example 3.

The pharmaceutical compositions of the present disclosure are formulated for oral administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media can be employed. For solid oral preparations such as, for example, powders, capsules, caplets, gelcaps, and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Oral pharmaceutical dosage forms can be solid, gel, or liquid. In some embodiments, the dosage form is a solid dosage form. In some embodiments, the solid dosage form is a pill, tablet, capsule, caplet, gelcaps, granules, powder, sachet, melting strip, or melting film. In some embodiments, the solid dosage form is coated. In some embodiments, the coating is an enteric coating, a sugar coating, or a film coating. In some embodiments, the solid dosage form is a coated particle, coated tablet, enterocoated tablet, or enterocoated capsule. In some embodiments, the solid dosage form is a pill or tablet. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric coated, sugar coated or film coated. In some embodiments, the pharmaceutical composition is formulated as a capsule. In some embodiments, the pharmaceutical composition is formulated as a powder, solution, or suspension (e.g., in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides), or is encapsulated in a capsule (gelatin or cellulose base capsule). Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with a combination of other ingredients known to those skilled in the art.

The pharmaceutical compositions of the present disclosure can contain, per dosage unit, e.g., tablet, capsule, powder, and the like, an amount of the active ingredient necessary to deliver an effective dose as described above.

In some embodiments, the pharmaceutical compositions of the present disclosure are formulated in unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg in the unit dosage form. For example, about 5 mg to about 175 mg, about 5 mg to about 150 mg, about 5 mg to about 125 mg, about 5 mg to about 100 mg, about 5 mg to about 75 mg,

about 5 mg to about 50 mg, about 5 mg to about 25 mg, about 25 mg to about 200 mg, about 25 mg to about 175 mg, about 25 mg to about 150 mg, about 25 mg to about 125 mg, about 25 mg to about 100 mg, about 25 mg to about 75 mg, about 25 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 175 mg, about 50 mg to about 150 mg, about 50 mg to about 125 mg, about 50 mg to about 100 mg, about 50 mg to about 75 mg, about 75 mg to about 200 mg, about 75 mg to about 175 mg, about 75 mg to about 150 mg, about 75 mg to about 125 mg, about 75 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 175 mg, about 100 mg to about 150 mg, about 100 mg to about 125 mg, about 125 mg to about 200 mg, about 125 mg to about 175 mg, about 125 mg to about 150 mg, about 150 mg to about 200 mg, about 150 mg to about 175 mg, or about 175 mg to about 200 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg to about 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg, about 10 mg, about 25 mg, about 35 mg, about 50 mg, about 65 mg, about 75 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, or about 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg in the unit dosage form. . In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg to 250 mg in the unit dosage form. For example, 5 mg to 175 mg, 5 mg to 150 mg, 5 mg to 125 mg, 5 mg to 100 mg, 5 mg to 75 mg, 5 mg to 50 mg, 5 mg to 25 mg, 25 mg to 200 mg, 25 mg to 175 mg, 25 mg to 150 mg, 25 mg to 125 mg, 25 mg to 100 mg, 25 mg to 75 mg, 25 mg to 50 mg, 50 mg to 200 mg, 50 mg to 175 mg, 50 mg to 150 mg, 50 mg to 125 mg, 50 mg to 100 mg, 50 mg to 75 mg, 75 mg to 200 mg, 75 mg to 175 mg, 75 mg to 150 mg, 75 mg to 125 mg, 75 mg to 100 mg, 100 mg to 200 mg, 100 mg to 175 mg, 100 mg to 150 mg, 100 mg to 125 mg, 125 mg to 200 mg, 125 mg to 175 mg, 125 mg to 150 mg, 150 mg to 200 mg, 150 mg to 175 mg, or 175 mg to 200 mg in the unit dosage form. In some embodiments, the

compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 25 mg to 125 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 75 mg to 150 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 5 mg, 10 mg, 25 mg, 35 mg, 50 mg, 65 mg, 75 mg, 90 mg, 100 mg, 125 mg, 150 mg, 175 mg, or 200 mg in the unit dosage form, or within a range defined by any of the preceding values. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 50 mg in the unit dosage form. In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt thereof, is present in an amount of 100 mg in the unit dosage form. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as a tablet. In some embodiments, the tablet is coated. In some embodiments, the pharmaceutical compositions of the present disclosure are formulated as capsules. In some embodiments, the pharmaceutical compositions are in sachet form. In some embodiments, the pharmaceutical compositions are in granule form.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in a dose of about 100 mg, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is administered in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

The daily dosage of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition as described in the present disclosure can be varied over a wide range from about 1.0 mg to about 10,000 mg per adult human per day, or higher, or any range therein. For oral administration, the compositions can be provided in the form of tablets containing, for example, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1.0 mg, about 2.5 mg, about 5.0 mg, about 10.0 mg, about 15.0 mg, about 25.0 mg, about 50.0 mg, about 75.0 mg, about 100 mg, about 150 mg, about 200 mg, about 250 or about 500 milligrams of the compound of Formula (I), or pharmaceutically acceptable salt thereof, for the symptomatic adjustment of the dosage to the subject to be treated. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from about 0.1 mg/kg to about 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from about 0.5 mg/kg to about 500 mg/kg, about 1.0 mg/kg to about 250 mg/kg, about 0.1 mg/kg to about 100 mg/kg, about 0.1 mg/kg to about 50.0 mg/kg of body weight per day, about 0.1 mg/kg to about 15.0 mg/kg of body weight per day, about 0.5 mg/kg to about 7.5 mg/kg of body weight per day, or any amount to range therein. In some embodiments, an effective amount of the compound of Formula (I), or pharmaceutically acceptable salt thereof, can be supplied at a dosage level of from 0.1 mg/kg to 1000 mg/kg of body weight per day, or any range therein, for example, the range can be from 0.5 mg/kg to 500 mg/kg, 1.0 mg/kg to 250 mg/kg, 0.1 mg/kg to 100 mg/kg, 0.1 mg/kg to 50.0 mg/kg of body weight per day, 0.1 mg/kg to 15.0 mg/kg of body weight per day, 0.5 mg/kg to 7.5 mg/kg of body weight per day, or any amount to range therein. A pharmaceutical composition as provided herein can be administered on a regimen of 1 to 4 times per day or in a single daily dose.

In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 25 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 50 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 75 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 100 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 150 mg, based on the weight of the free base. In some embodiments, the daily dose of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is about 200 mg, based on the weight of the free base.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 25 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 50 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 100 mg, based on the weight of the free base.

In some embodiments, the daily dose of the pharmaceutical composition is about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the pharmaceutical composition is about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the daily dose of the

pharmaceutical composition is about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the pharmaceutical composition is administered twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some

embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the compound of Formula (I), or a pharmaceutically acceptable salt thereof, twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base. In some embodiments, the method comprises administering the pharmaceutical composition twice daily in a dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

Factors associated with the particular subject being treated, including subject age, weight, diet, and time of administration, can result in the need to adjust dosages. In some embodiments, the subject is a human adult. In some embodiments, the subject is a pediatric subject.

One skilled in the art will recognize that both *in vivo* and *in vitro* trials using suitable, known, and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder. One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy subjects and/or those suffering from a given disorder, can be completed according to methods well known in the clinical and medical arts. For example, determining proper dosages for pediatric subjects can be determined using known methods, including weight, age, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account subject age, ontogeny of the clearance pathways that a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and body surface area (BSA).

In some embodiments, the pharmaceutical compositions of the present disclosure are stable for at least 3 months. In some embodiments, the pharmaceutical compositions are stable for at least 6 months. In some embodiments, the pharmaceutical compositions are stable for at least 9 months. In some embodiments, the pharmaceutical compositions are stable for at least 12 months. For example, the compositions do not exhibit a change (e.g., greater than 5%) in appearance, pH, percent impurities, activity (as measured by in vitro assays), or osmolarity over time, e.g., at least 3 months, 6 months, 9 months, or at least 12 months as compared to the original composition after manufacturing. In some embodiments, the pharmaceutical compositions do not exhibit a significant change, as defined by the International Conference

on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in one or more of appearance, pH, percent impurities, activity (as measured by *in vitro* assays), or osmolarity over time, e.g., at least 12 months as compared to the original pharmaceutical composition after manufacturing.

Kits

Also provided are kits. Typically, a kit includes one or more pharmaceutical compositions as described herein, e.g., a pharmaceutical composition containing, e.g., a spray-dried dispersion as described in Examples 1-4, or the formulation described in Example 9. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering the pharmaceutical composition as provided herein, and directions for use of the kit (e.g., instructions for treating a subject). In some embodiments, the kit can include a pharmaceutical composition as described herein and a label that indicates that the contents are to be administered to a subject with congenital adrenal hyperplasia. The actual dose of the compound of Formula (I), or pharmaceutically acceptable salt thereof, provided herein depends on the specific formulation, the weight of the patient, and on the condition to be treated.

EXAMPLES

Example 1: Spray-dried dispersion formulations containing the compound of Formula (I) and various polymers

Spray-dried dispersion formulations

A series of spray-dried dispersion (SDD) formulations containing the compound of Formula (I) and a polymer were prepared. The SDD formulations included: (1) 10% compound of Formula (I)/90% hydroxypropylmethylcellulose acetate succinate-L (HPMCAS-L); (2) 25% compound of Formula (I)/75% HPMCAS-L; (3) 40% compound of Formula (I)/60% HPMCAS-L; (4) 25% compound of Formula (I)/75% polyvinyl pyrrolidone vinyl acetate 64 (PVP/VA 64); (5) 25% compound of Formula (I)/60% Cabosil (fumed silica)/15% HPMCAS-L; (6) 25% compound of Formula (I)/75% HPMCAS-M; and (7) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100).

The PVP/VA polymer was a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate with a ratio of 60:40 by weight 1-vinyl-2-pyrrolidone:vinyl acetate with an average molecular weight of 45,000-70,000 (copovidone, sold as Kollidon® VA 64, BASF, Florham Park, NJ). The HPMCAS was a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose that was either grade L (HPMCAS-L), with an acetyl content of 5-9%, a succinoyl content of 14-18%, a methoxyl content of 20-24%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan); or grade M (HPMCAS-M), with an acetyl content of 7-11%, a succinoyl content of 10-14%, a methoxyl content of 21-25%, and a hydroxypropoxy content of 5-9% (sold by Shin-Etsu, Japan).

Dissolution performance

Dissolution performance of several of the SDD formulations described above was tested (see FIG. 1). 1000 µgA/mL of each SDD was tested in 0.5 wt% simulated intestinal fluid (SIF) in PBS, pH 6.5. Samples were tested at 5, 10, 20, 45, 90, and 1200 minutes. A lipid formulation containing 10% of the compound of Formula (I) was used as a control. The results are shown in Table 4, below.

Table 4. Dissolution data of various SDDs

Sample	C_{max90} (µg/mL)	AUC_{90} (min*µg/mL)	C_{max90} (µg/mL)	$Ultra_{90}$ (µg/mL)	C_{1200} (µg/mL)	$Ultra_{1200}$ (µg/mL)
2	762	66,080	743	210	671	166
4	322	27,330	306	109*	268	199
6	718	62,240	708	202	632	217
7	742	60,600	742	113*	674	194
Control	802	69,580	800	253	799	270

*Large variability between replicates, high value discarded

Non-sink dissolution

A membrane flux assay was performed (see, e.g., Stewart et al., Mol. Pharm. (2017) 14:2032-2046) and non-sink dissolution data was collected for several of the SDD formulations described above and compared to the compound of Formula (I) and several reference formulations, including a semi-solid lipidic formulation (Reference Formulation 1) and two self-emulsifying drug delivery system (SEDDS) formulations (Reference Formulations 2 and 3). The components of the Reference Formulations are shown in Table 5, below, and include, in addition to the compound of Formula (I), caprylic/capric triglyceride (Labrafac® Lipophile, Gattefossé, France); propylene glycol dicrapolate/dicaprate (Labrafac® PG, Gattefossé, France); oleoyl polyoxyl-6 glycerides (Labrafil® M 1944 CS, Gattefossé, France); polysorbate 20; polyoxyl castor oil (Kolliphor® RH 40, BASF, Germany); polyoxyl 15 hydroxystearate (Kolliphor® HS 15, BASF, Germany); lauroyl polyoxyl-32 glycerides (Gelucire® 44/14, Gattefossé, France); d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS); and diethylene glycol monoethyl ether (Transcutol®, Gattefossé, France).

Table 5. Reference formulations (capsules)

Formulation (mg/caps)	Ref. Formulation 1	Ref. Formulation 2	Ref. Formulation 3
Formula (I)	50.0	50.0	50.0
Labrafac® Lipophile	196.0	100.0	100.0
Labrafac® PG	102.0	-	-
Labrafil® M 1944 CS	-	135.0	46.0
Polysorbate 20	-	-	89.9
Kolliphor® RH 40	-	-	100.0
Kolliphor® HS 15	-	165.0	-
Gelucire® 44/14	95.0	-	-
TPGS	57.0	-	65.0
Transcutol®	-	50.0	50.0
Total	500.0	500.0	500.0

The assay measured the flux across simulated gastric and intestinal walls via UV spectroscopy (μDiss ProfilerTM, Pion Inc., Billerica, MA). Briefly, the assay was performed as follows. A vertical membrane flux cell consisting of a donor compartment and a receiver compartment, and separated by an Accurel PP 1E (55% porous, 100 μm thickness) polypropylene membrane (3M, Maplewood, MN) (FIG. 2), was impregnated with 50 μL of Pion GIT-0 lipid solution consisting of 20% w/w phospholipid dissolved into dodecane (Pion Inc., Billerica, MA) and attached to the receiver vessel. Both the donor and receiver compartments were agitated by magnetic stirring. The receiver compartment contained a plastic spacer and grating to elevate the stir bar above the membrane. Samples were introduced to the donor vessel by pre-weighing directly into the donor vessel and subsequently adding dissolution medium. Once the dissolution medium was added to the donor vessel, the receiver vessel was inserted into the donor vessel and suspended vertically 5 mm above the donor compartment by a plastic sleeve. For this assay, the simulated gastric (feed) media was 0.1 N HCl, pH 2 and included 200 μgA/mL of each SDD, and the simulated intestinal (receiver) media was 0.5 wt% SIF in PBS, pH 6.5 and included 100 μgA/mL of each SDD. The temperature for the assay was maintained at 44.5°C. UV probes (10 mm path length) connected to a Rainbow UV spectrometer (Pion Inc.) system were used to determine the apparent drug

concentration in the receiver vessels. Samples of the donor compartment were removed with a disposable pipet for centrifugation followed by HPLC and DLS analysis of the supernatant. The results are shown in FIG. 3 and Table 6, below.

Table 6. Non-sink dissolution data

Sample	C_{maxGB} (µg/mL)	$C_{max90\ IB}$ (µg/mL)	$AUC_{4\text{-}90IB}$ (min*µg/mL)	C_{90} (µg/mL)	$Ultra_{90}$ (µg/mL)	C_{1200} (µg/mL)
Formula (I)	0	1	10	0	0	3
1	6	80	6,800	80	79	90
2	17	74	6,240	73	73	86
4	6	4	200	4	5	36
5	23	55	3,180	55	54	83
6	35	71	6,070	71	77	83
Ref. Formulation 1	205	109	9,050	109	-	-
Ref. Formulation 2	249	120	10,160	120	-	-
Ref. Formulation 3	218	107	9,100	107	-	-

The membrane flux of 1 mg/mL gastric barrier/intestinal barrier (GB/IB) 0.5 wt% SIF doses of the compound of Formula (I) and spray-dried dispersions (2) 25% compound of Formula (I)/75% HPMCAS-L and (4) 25% compound of Formula (I)/75% PVP/VA 64 were also determined. The results are shown in FIG. 4 as receiver concentration vs. time and flux vs. time (smoothed derivative of receiver concentration x volume/surface area).

Example 2: Characterization of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% of a polyvinyl pyrrolidone vinyl acetate (PVP/VA) polymer

SDD stability screening

Several of the SDDs described in Example 1 were tested for chemical and physical stability. Wet SDD stability studies were performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 7 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 7. Wet SDD stability data

Retention time (min)			11.04	16.79	17.26	30.94	32.26			
Relative retention time			0.34	0.52	0.53	0.96	1.00			
	Storage temp	**Timepoint**						**Total impurities**	**Potency (mgA/g)**	**Std Dev**
Ref. Std.						0.37	99.63	0.37		
Formula (I)						0.26	99.74	0.26		
Sample 1		initial		0.13	0.16	0.25	99.46	0.54	100	1.3
	5°C	1 week		0.03	0.03	0.26	99.69	0.31	99	0.0
		2 weeks		0.12	0.16	0.28	99.45	0.55	99	0.5
	25°C	1 week		0.03	0.04	0.26	99.67	0.33	99	0.3
		2 weeks		0.21	0.27	0.28	99.24	0.76	98	0.8
Sample 2		initial	<LOQ	0.07	0.08	0.26	99.59	0.41	247	0.3
	5°C	1 week	<LOQ	0.02	0.03	0.26	99.70	0.30	248	1.3
		2 weeks	<LOQ	0.22	0.27	0.27	99.24	0.76	246	0.3
	25°C	1 week	<LOQ	0.02	0.03	0.26	99.69	0.31	248	0.9
		2 weeks	<LOQ	0.23	0.28	0.26	99.23	0.77	246	1.4

LOQ = limit of quantification

Solution stability studies were also performed, with samples stored at both 5°C and 25°C. Measurements were taken after 1 week and 2 weeks of storage. The results are shown in Table 8 below. The column with a retention time of 32.36 min correlates with the compound of Formula (I).

Table 8. SDD solution stability data

Retention time (min)			31.51	32.26	
Relative retention time			0.97	1.00	
	Storage temp	**Timepoint**			**Total impurities**
Ref. Std.			0.74	99.26	0.74
Formula (I)			0.26	99.74	0.26
Sample 1		initial	0.33	99.67	0.33
	5°C	2 weeks	0.29	99.71	0.29
	25°C	2 weeks	0.38	99.62	0.38
Sample 2		initial	0.25	99.75	0.25
	5°C	2 weeks	0.26	99.74	0.26
	25°C	2 weeks	0.33	99.67	0.33

Stability studies were also performed for the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64, with samples stored at both 5°C (closed with desiccant), 25°C (60% RH, closed with desiccant), and 30°C (65% RH, closed with desiccant). Measurements were taken after storage for 1 month, 2 months, 3 months, 6 months, and 12 months. No change in purity was observed after 12 months of storage. The results are shown in Table 9 below. The column with a retention time of 30.2 min correlates with the compound of Formula (I).

Table 9. SDD stability data

Retention time (min)			28.7	30.2		
Relative retention time			0.95	1.00		
	Storage conditions	**Timepoint**			**Total impurities**	**Potency (mgA/g)**
Crystalline Formula (I)			0.26	99.74	0.26	1001
Sample 4 (25% Formula (I):75% PVP/VA 64)		initial	0.26	99.74	0.26	245
	5°C (closed w/ desiccant)	1 month	0.25	99.75	0.25	247
		2 months	0.25	99.75	0.25	244
		3 months	0.26	99.74	0.26	246
		6 months	0.25	99.75	0.25	245
		12 months	0.25	99.75	0.25	248
	25°C/60% RH (closed with desiccant)	1 month	0.25	99.75	0.25	245
		2 months	0.25	99.75	0.25	247
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.75	0.25	242
		12 months	0.25	99.75	0.25	245
	30°C/65% RH (closed with desiccant)	1 month	0.25	99.75	0.25	249
		2 months	0.25	99.75	0.25	242
		3 months	0.25	99.75	0.25	246
		6 months	0.25	99.73	0.25	243
		12 months	0.25	99.75	0.25	242

While Samples 1 and 2 showed degradation after about 2 weeks of storage, the SDD containing 25% of the compound of Formula (I) and 75% PVP/VA 64 (Sample 4) was found to be both chemically and physically stable and was further screened and characterized as described below.

25% Formula (I)/75% PVP/VA 64 SDD process parameter screening manufacture Round 1

The 25% Formula (I)/75% PVP/VA 64 SDD was prepared on a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The manufacturing summary is shown in Table 10, below.

Table 10. Manufacturing summary of process parameters

Formulation	25% Formula (I):75% PVP/VA 64
Solids Loading (wt%)	10
Batch Size (kg)	1.5
Solvent	Acetone
Atomizer (Pressure Swirl)	SK 80-16
Solution Flow-rate (g/min)	160
Atomization Pressure (psig)	480
Inlet Temperature (°C)	94
Outlet Temperature (°C)	40
Calculated Outlet Acetone Saturation (% RS)	6.2
Dry Yield (%)	73

Based on the 73% yield observed in the first round of process screening, three sprays were performed to investigate the effect of reducing solution throughput and outlet temperature on product yield. All sprays were conducted at a reduced flow-rate of 110 g/min. The outlet temperature was varied at 40°C (Lot A), 35°C (Lot B), and 30°C (Lot C). The outlet temperature was decreased while maintaining a low outlet acetone saturation to increase the difference between the chamber outlet temperature and the wet SDD T_g, thus improving product yields. The spray dryer chamber and outlet ductwork were cleaned between all manufactures. A manufacturing summary is shown in Table 11.

Table 11. Manufacturing summary for process parameters (1.5 kg batch size)

Description	Low Flow-Rate	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Lower Outlet Temperature
Lot	A	B	C
Solids Loading (wt%)	10	10	10
Batch Size (kg)	1.5	1.5	1.5
Solvent	Acetone	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110	110
Atomization Pressure (psig)	275	285	285
Inlet Temperature (°C)	79	72	63
Outlet Temperature (°C)	40	35	30
Calculated Outlet Acetone Saturation (% RS)	4.3	5.2	6.4
Calculated wet SDD T_g (°C)	72	71	69
Dry Yield (%)	55	80	43

The conditions used for Lot B were found to give the highest yield. One additional spray was then performed at the same processing conditions as Lot B while increasing the batch size from 1.5 kg to 3.5 kg to evaluate process consistency and to determine if product yield would continue to improve over time. The averaged process conditions for this lot are shown in Table 12.

Table 12. Manufacturing summary of process parameters (1.5 kg and 3.5 kg batch sizes)

Description	Low Flow-Rate/Low Outlet Temperature	Low Flow-Rate/Low Outlet Temperature/Larger Batch Size
Lot	B	D
Solids Loading (wt%)	10	10
Batch Size (kg)	1.5	3.5
Solvent	Acetone	Acetone
Atomizer (Pressure Swirl)	Steinen A75	Steinen A75
Solution Flow-Rate (g/min)	110	110
Atomization Pressure (psig)	285	285
Inlet Temperature (°C)	72	72
Outlet Temperature (°C)	35	35
Calculated Outlet Acetone Saturation (% RS)	5.2	5.2
Calculated wet SDD T_g (°C)	71	71
Dry Yield (%)	80	84

The 1.5 kg batch size (Lot D) was sprayed with an 84% yield compared to the 80% yield of the 3.5 kg batch (Lot B).

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25% Formula (I)/75% PVP/VA 64 SDD process parameter screening characterization

The 25% Formula (I)/75% PVP/VA 64 SDDs manufactured to evaluate processing parameters were characterized for powder properties, performance, and physical and chemical
10 properties. Testing included particle size distribution by Malvern, determination of bulk and tapped density, microcentrifuge dissolution, modulated differential scanning calorimetry (mDSC), powder x-ray diffraction (PXRD), scanning electron microscope (SEM), and assay and related substances. The results did not show any significant differences between the lots.

The particle size distribution (PSD) and tabulated powder properties data of the 25%
15 Formula (I)/75% PVP/VA 64 SDDs are shown in Table 13. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have a very similar PSD with a D_{50} of approximately 16 µm. All 25% Formula (I)/75% PVP/VA 64 SDDs were observed to have low bulk and tapped densities.

Table 13. Powder properties of process parameter screening PVP/VA-64 SDDs

Sample	Lot	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	$D_{(3,2)}$ (µm)	$D_{(4,3)}$ (µm)	Span	Bulk density (g/mL)	Tapped density (g/mL)
40°C Outlet	A	5	15	34	8	17	1.93	0.12	0.25
35°C Outlet	B	5	16	36	9	19	1.97	0.11	0.23
30°C Outlet	C	5	15	32	7	17	1.86	0.12	0.27
35°C Outlet, 3.5 kg batch	D	5	16	38	9	19	1.98	0.12	0.24

The 3.5 kg batch size lot was analyzed and compared to process parameter Lot A. Dissolution performance was similar for each of these lots. Dissolution was rapid to C_{max} and high free drug was sustained through 90 minutes. These data are shown in Table 14.

Table 14. Dissolution performance of Lot A (1.5 kg batch size) vs. Lot D (3.5 kg batch size)

Sample	C_{max90} (µg/mL)	AUC_{90} (min*µg/mL)	C_{90} (µg/mL)	$Ultra_{90}$ (µg/mL)
Lot A	447	37,740	437	319
Lot D	437	37,120	433	301

The 25% Formula (I)/75% PVP/VA 64 SDDs were also evaluated by DSC, PXRD, and SEM. The DSC thermograms showed a single T_g at 84°C, indicating homogeneous dispersions. PXRD diffractograms showed no evidence of crystals in the SDDs. SEM images showed inflated sphere morphology with some broken particles and some very small particles.

Additional testing on Lot B was carried out, which included assessing the chemical/physical stability of both spray solution and SDD prior to secondary drying (wet

SDD) to establish maximum in-process hold times. Residual acetone concentration as a function of secondary drying time in a convection tray dryer was also evaluated to nominate tray drying conditions to ensure the SDD is dried below International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for acetone.

Residual acetone content as a function of drying time was assessed by drying wet SDD in a tray dryer and collecting samples over a 24-hour period. Wet SDD was dried at 40°C/15% relative humidity (RH) and was observed to dry below ICH acetone guidelines (0.5 wt%, 5000 ppm) by four hours.

Spray solution hold time was determined by making up a representative solution that contained 2.5 wt% compound of Formula (I), 7.5 wt% PVP/VA 64, and 90 wt% acetone. These solutions were analyzed initially for related substances. and then aged at 5°C and 25°C. Aliquots were taken and analyzed for related substances periodically for 14 days. Results showed no change in impurity profile at either condition through 14 days.

Wet SDD was analyzed for impurities after storage at 5°C and 25°C for 1 and 2 weeks and compared to the impurity profiles of the ingoing compound of Formula (I) and the SDD that was secondarily dried immediately after spray drying. The impurity profiles were similar to that of the initial dried sample and the ingoing compound of Formula (I) through 2 weeks of storage.

The wet SDD stability samples were characterized for physical stability by DSC, PXRD, and SEM. DSC thermograms showed a single T_g at 81°C, indicative of a homogeneous dispersion with no phase separation. The PXRD diffractograms did not show any evidence of crystals after storage at either condition. SEM images showed a typical morphology of mostly inflated spheres with some broken particles.

Example 3: Preparation of a 1000 g batch of a spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64

A 1000 g batch of the spray-dried dispersion containing 25% of the compound of Formula (I) and 75% PVP/VA 64 was prepared as described in Example 2 for the 1.5 kg and 3.5 kg batches. Briefly, acetone (90% (w/w) of the total mixture) was added to the mixing tank followed by the addition of 250.0 g of the compound of Formula (I) (2.5% (w/w) of the total mixture). The mixture was mixed for 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

The PVP/VA 64 (750.0 g, 7.5% (w/w) of the total mixture) was then added and the mixture was stirred for an additional 30 minutes in the dark at a temperature range of 15°C to 27°C. At the end of the mixing period, the solution was clear and free of undissolved solids.

The solution was pumped and atomized in a drying chamber. The spray-dried dispersions were prepared in a Pharmaceutical Spray Dryer with 100 kg/hr drying gas capacity (PSD-1). The inlet temperature was set at 75°C (varied between 60°C-90°C). The outlet temperature was set at 35°C (varied between 32°C-38°C). The feed pressure was set at 280 psig (varied between 230-330 psig). The feed rate was set at 110 g/min (varied between 90-130 g/min). The spray dried powder was then dried in a convection tray dryer with a bed depth of ≤ 2.5 cm at 40°C (±5°C) and 15% relative humidity (±10%) for 24 hours under amber light. The residual acetone after drying was < 0.5 wt% (5000 ppm). FIG. 5 is a flow diagram of the manufacturing process.

Example 4: Preparation of spray-dried dispersion formulations of the compound of Formula (I) for clinical use

The spray-dried dispersion (SDD) containing 25% compound of Formula (I) and 75% PVP/VA 64, prepared as described above, was formulated as a suspension or a capsule for clinical use.

Suspension preparation

A suspension that contained 50 mg of the SDD was prepared as follows. A 30 mL amber dosing bottle was tared on a balance. 200.0 mg SDD (50 mgA) ± 5% was then weighed into the dosing bottle. Using a 10-mL syringe, 5.0 mL of water (purified, USP) was added to the dosing bottle and the bottle was capped and shaken moderately for 30 seconds. The SDD suspension was stored in an amber vial at 2-8°C prior to use, and dosed within 24 hours of preparation.

Capsule preparation

An empty hard gelatin capsule, size 0 (Capsugel, Morristown, NJ), was placed on a balance and the weight was recorded. 200.0 mg SDD (50 mgA) ± 5% was then weighed onto weigh paper or an equivalent. All contents were transferred to the capsule using a ProFunnel device for Size 0 capsules. The filled capsule was placed on the balance and the weight was recorded. The weight of the empty capsule was subtracted from the filled weight, ensuring that the weight of the SDD within the capsule was 200.0 mg SDD ± 5%, or from 190.0 mg to 210.0 mg. The capsule was securely closed with the head, assuring it clicked into place. The capsules

were stored in an amber vial at 2-8°C prior to use, and were dosed within 24 hours of preparation.

Example 5: Dog relative bioavailability and food effect study

Four spray-dried dispersions (SDDs), formulated in 0.25% methylcellulose as a suspension, were prepared: (1) 25% compound of Formula (I)/75% HPMCAS-L; (2) 10% compound of Formula (I)/90% HPMCAS-L; (3) 25% compound of Formula (I)/75% methyl methacrylate copolymer (1:1) (Eudragit® L100); and (4) 25% compound of Formula (I)/75% PVP/VA 64. A clinical capsule formulation was prepared as a reference formulation (Reference Formulation 1 from Table 5, above).

Dogs (two cohorts, six dogs in each) were dosed in six sessions, including fasted state sessions and fed sessions (high fat diet), with 50 mg dose of one of the SDDs or reference per dog in a 3-way crossover design. Each session had a 3-day washout in between. All formulations were well tolerated. The study design is shown in Table 15, below.

Table 15. Study design

Cohort 1	**Session 1 (Fasted)**	**Session 2 (Fed)**	**Session 3 (Fasted)**	**Session 4 (Fed)**	**Session 5 (Fasted)**	**Session 6 (Fed)**
Dog 1001	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 1002	Reference	Reference	SDD 1	SDD 1	SDD 2	SDD 2
Dog 2001	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 2002	SDD 1	SDD 1	SDD 2	SDD 2	Reference	Reference
Dog 3001	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Dog 3002	SDD 2	SDD 2	Reference	Reference	SDD 1	SDD 1
Cohort 2	**Session 1 (Fasted)**	**Session 2 (Fed)**	**Session 3 (Fasted)**	**Session 4 (Fed)**	**Session 5 (Fasted)**	**Session 6 (Fed)**
Dog 4001	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 4002	Reference	Reference	SDD 3	SDD 3	SDD 4	SDD 4
Dog 5001	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 5002	SDD 3	SDD 3	SDD 4	SDD 4	Reference	Reference
Dog 6001	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3
Dog 6002	SDD 4	SDD 4	Reference	Reference	SDD 3	SDD 3

The area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), the apparent terminal half-life ($t_{½}$), and the time to achieve maximum plasma concentration (t_{max}) were calculated. Results are shown in Table 16, below, and in FIGS. 6A and 6B.

Table 16. Pharmacokinetic results

Cohort	Form	Fasted [Mean (%CV)]		Fed [Mean (%CV)]		Ratio of Fed/Fasted [Mean (%CV)]	
		C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{inf} (hr*ng/mL)	C_{max}	AUC
1 (N=4)*	Ref	652 (55.5)	5170 (69.4)	3650 (19.5)	20100 (22)	6.9 (48)	5.5 (69.2)
	SDD 1	524 (62.7)	2870 (62.9)	5760 (25.6)	22800 (14.6)	15.4 (66.9)	8 (89.6)
	SDD 2	487 (45.7)	3950 (26.4)	4220 (27.4)	18100 (26.8)	16.5 (40.7)	6.3 (34.6)
2 (N=6)	Ref	854 (40.2)	5520 (59.1)	4220 (27.4)	18100 (26.8)	5.8 (46.5)	4.1 (49.2)
	SDD 3	453 (28.3)	2830 (21.6)	5320 (13.5)	23800 (26.1)	12.6 (30.3)	8.6 (22.2)
	SDD 4	353 (20.1)	1840 (21.9)	3060 (20.7)	17200 (20.5)	8.9 (29.3)	8.4 (46.1)

*Animals 2001 and 2002 were excluded from summary statistics due to emesis in all 3 fed sessions, which resulted in notably lower exposures

The results showed that $t_{1/2}$ and t_{max} were similar among the formulations, and comparable between the fed and fasted states. Under the fed state with a high fat meal, exposures increased and inter-animal variability decreased. The food effect was more notable with the spray-dried dispersion formulations, especially for peak exposure (C_{max}).

Compared to the reference form, SDD 4 (25% compound of Formula (I)/75% PVP/VA 64) appeared to have lower inter-animal variability, lower exposures under the fasted state, and slightly lower C_{max} but relatively comparable AUC in the fed state.

Example 6: Phase 1 study to evaluate the pharmacokinetics, effect of food on pharmacokinetics, and safety of the compound of Formula (I) in healthy adult subjects

The present study was designed to evaluate the pharmacokinetics (PK) of the compound of Formula (I) as well as to evaluate the effect of a fed condition on the PK of the compound of Formula (I). The 50 mg dose was chosen for this study because it was within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study were: to evaluate the PK of the compound of Formula (I) 50 mg in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg.

Study Design

This was a Phase 1, open-label, randomized, 2-period crossover study of the PK and the effect of food on the PK of the compound of Formula (I) in 16 healthy male and female adult subjects, 18 to 55 years of age.

After providing informed consent, subjects were screened for eligibility to participate in the study up to 28 days prior to Day 1 of treatment period 1. Eligible subjects were admitted to the clinical unit on Day -1 and randomized to 1 of the 2 treatment sequences (16 subjects [8 males and 8 females]; see Table 17, below). On Day 1 of each treatment period, subjects received a single dose of the compound of Formula (I) 50 mg under fasted or fed conditions. There were 21 days between doses.

Table 17. Treatment sequences

Treatment sequence	Treatment period 1	Treatment period 2
1	Formula (I) – fasted	Formula (I) – fed
2	Formula (I) – fed	Formula (I) – fasted

Subjects were required to fast for at least 4 hours before check-in on Day -1. In the fasted condition, subjects were required to fast overnight for at least 10 hours prior to dosing and continued to fast for an additional 4 hours after dosing. In the fed condition, subjects were required to fast overnight for at least 10 hours and then ingest a liquid dietary supplement with study drug (liquid dietary supplement was consumed within 30 minutes) and not consume any other food for 4 hours after dosing. During both treatment periods, water was not permitted for

1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing. Vanilla-flavored Ensure Plus® was used as the liquid dietary supplement.

On Day 1 of each treatment period, subjects were dosed with the compound of Formula (I) 50 mg. Blood samples were collected for PK analysis over a period of 36 hours during the in-house stay. Subjects remained in the unit on the day of dosing and were discharged on Day 2 of each treatment period, following completion of all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects returned to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1, subjects arrived at the site and had Day 21 assessments completed in the evening, and they stayed overnight at the site and began Day 1 of treatment period 2 the following day. A final follow-up study visit was conducted on Day 22 of treatment period 2 (21 ± 2 days after treatment period 2 dosing) or upon early termination.

During each treatment period, blood samples for PK analysis were collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

Safety assessments (including clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms (ECGs)) were conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications were monitored throughout the study. FIG. 7 illustrates the study design.

Test product, dose and mode of administration

The compound of Formula (I) was supplied as an encapsulated, lipidic semi-solid containing 50 mg of the compound of Formula (I) as free base equivalent for oral administration. Subjects swallowed a single capsule with approximately 240 mL of water in the fasted condition. Subjects swallowed a single capsule with a liquid dietary supplement (Ensure Plus® [237 mL container]) with up to an additional 120 mL of water in the fed condition.

Duration of treatment

The duration of study participation for each adult subject was approximately 10 weeks, including up to 28 days of screening, 2 days of dosing separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 2.

Criteria for Evaluation

Pharmacokinetics

The following plasma PK parameters were calculated for the compound of Formula (I):

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0-tlast}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours (AUC_{0-24})
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0-\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of the hydroxylated metabolite of the compound of Formula (I) to the parent drug the compound of Formula (I)

The following plasma PK parameters were calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Safety

Safety was monitored throughout the study and included the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical Methods

Pharmacokinetic parameters were calculated using noncompartmental methods and summarized by condition (fed or fasted) using descriptive statistics. Two-sided 90% confidence intervals were calculated for the ratio under the fed condition vs. under the fasted condition for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I).

Safety data were summarized with descriptive statistics.

Pharmacokinetics

Pharmacokinetic assessments

PK plasma samples for analyses of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were collected at the following times during each treatment period:

- Day 1: within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5,6, 7, 8, 9, 10, 12, and 16 hours after dosing.
- Day 2: approximately 24 and 36 hours after dosing.
- Day 8: approximately 168 hours after dosing.
- Day 15: approximately 336 hours after dosing.
- Approximately 504 hours after dosing (for treatment period 1, this sample was collected in the morning at least 30 minutes prior to the predose sample on Day 1 of treatment period 2).
- Final study visit for subjects who terminate early: 1 sample.

Blood samples on Day 1 were collected within 5 minutes of the scheduled sampling times (other than the predose sample). Blood samples on Days 2, 8, and 15 were collected within 2 hours of the scheduled sampling time. The 504 hour blood sample for treatment period 2 had a ± 2-day window. A PK sample was to be collected from subjects who terminated early. The exact time of sampling in hour and minutes was recorded.

Bioanalytical methods

Plasma samples were analyzed for the compound of Formula (I) and for its hydroxylated metabolite by inVentiv Health, Princeton NJ, in compliance with Good Laboratory Practice (GLP) and relevant Standard Operating Procedures (SOPs).

The concentrations of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) were quantified in plasma samples according to validated

methods using tandem mass spectrometry in positive ion mode. This method was validated for the analysis of the compound of Formula (I) and the hydroxylated metabolite of the compound of Formula (I) in 25.0 µL dipotassium ethylenediaminetetraacetic acid (K_2-EDTA) human plasma samples over concentration ranges of 5.00 to 2500 ng/mL and 0.500 and 250 ng/mL, respectively. All analytical results were within acceptable limits. Incurred sample reanalysis (ISR) was successfully conducted in this study for both analytes.

Results

Pharmacokinetic results

Eight male and eight female subjects were enrolled. The mean age was 37.1 years (range, 21 to 55 years). The majority of subjects were White (93.8%) and of Hispanic ethnicity (81.3%). The mean weight at screening was 160.28 lbs (range, 102.0 to 222.2 lbs) and mean BMI was 25.50 kg/m^2 (range, 20.7 to 30.5 kg/m^2). The randomization was well balanced with respect to demographics and baseline characteristics.

All 16 subjects were included in the safety analysis set. No subjects were excluded from the safety analysis set and no subject had his or her PK data excluded from analysis.

The mean plasma concentration versus time profiles for the compound of Formula (I) under fasted and fed conditions are presented in FIGS. 8A and 8B, respectively. The compound of Formula (I) was slowly absorbed after oral administration in both fasted and fed conditions. Mean plasma concentrations were lower in the fasted than in the fed condition.

PK parameters for the compound of Formula (I) after treatment with the compound of Formula (I) under fasted and fed conditions are summarized in Table 18, below, where AUC_{0-24}=area under the plasma concentration vs. time curve from 0 to 24 hours, $AUC_{0-tlast}$=AUC from 0 hours to last measurable concentration, $AUC_{0-\infty}$=AUC from 0 hours extrapolated to infinity, CL/F=apparent systemic clearance after oral administration, CV=coefficient of variation, C_{max}=maximum plasma concentration, CV(%)=coefficient of variation, max=maximum, min=minimum, MRT=apparent mean residence time, PK=pharmacokinetic, SD=standard deviation, $t_{½}$=apparent terminal half-life, T_{lag}=delay time between time of dosing and time of appearance of measurable test article, t_{max}=time to maximum plasma concentration, VZ/F=apparent volume of distribution during the terminal phase after oral administration.

The PK data for t_{max}, T_{lag}, $t_{½}$, MRT, and Vz/F were rounded to 2 significant figures and all other parameters (AUC_{0-24}, $AUC_{0-tlast}$, $AUC_{0-\infty}$, C_{max}, and CL/F) were rounded to 3

significant figures. The last significant figure was rounded up if the digit to the right of it was ≥5, and was rounded down if the digit to the right of it was ≤4.

Table 18. Summary of Formula (I) PK parameters (safety analysis set)

Parameter Statistic	Fasted Formula (I) (50 mg) (N=16)	Fed Formula (I) (50 mg) (N=15)
$AUC_{0\text{-}24}$ (ng×hr/mL) Mean (SD) Geometric CV%	 5590 (2230) 32.7	 9950 (2540) 26.2
$AUC_{0\text{-}tlast}$ (ng×hr/mL) Mean (SD) Geometric CV%	 8020 (5110) 53.6	 16200 (5450) 39.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL) Mean (SD) Geometric CV%	 9440 (2990) [n=7] 39.7	 17800 (4990) [n=12] 28.1
C_{max} (ng/mL) Mean (SD) Geometric CV%	 731 (301) 36.6	 1550 (392) 24.2
t_{max} (hours) Median (min, max)	 6.0 (3.0, 6.0)	 5.0 (3.0, 6.0)
T_{lag} (hours) Mean (SD)	 0.63 (0.22)	 0.94 (0.37)
$t_{½}$ (hours) Mean (SD) Geometric CV%	 33 (17) [n=7] 99	 42 (6.8) [n=12] 15
MRT (hours) Mean (SD) Geometric CV%	 28 (11) [n=7] 49	 30 (5.0) [n=12] 16
CL/F (L/hr) Mean (SD) Geometric CV%	 6.0 (2.7) [n=7] 40	 3.0 (0.82) [n=12] 28
VZ/F (L) Mean (SD) Geometric CV%	 240 (120) [n=7] 67	 180 (57) [n=12] 30

As seen in Table 18, above, administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0\text{-}\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ng×hr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0\text{-}tlast}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when

administered with food. The upper and lower 90% confidence interval (CI) bounds for both C_{max} (187.4% and 255.1%, respectively) and $AUC_{0\text{-tlast}}$ (182.9% and 253.1%, respectively) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure.

Frequency distribution of T_{lag} and t_{max} values are presented in Table 19 and Table 20, respectively. Spaghetti plots for the compound of Formula (I) $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} are shown in FIGS. 9A, 9B, and 9C, respectively.

Table 19. Frequency distribution of plasma Formula (I) T_{lag} values by treatment (safety analysis set)

T_{lag} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
0.50	n (%)	11 (68.8%)	3 (20.0%)
0.53	n (%)	1 (6.3%)	0 (0.0%)
0.55	n (%)	0 (0.0%)	1 (6.7%)
1.00	n (%)	4 (25.0%)	8 (53.3%)
1.02	n (%)	0 (0.0%)	1 (6.7%)
1.03	n (%)	0 (0.0%)	1 (6.7%)
2.00	n (%)	0 (0.0%)	1 (6.7%)

Table 20. Frequency distribution of plasma Formula (I) T_{max} values by treatment (safety analysis set)

T_{max} (hr)	Statistic	Fasted (Formula (I) 50 mg) (N=16)	Fed (Formula (I) 50 mg) (N=15)
3.00	n (%)	1 (6.3%)	2 (13.3%)
4.02	n (%)	1 (6.3%)	0 (0.0%)
5.00	n (%)	4 (25.0%)	8 (53.3%)
5.03	n (%)	0 (0.0%)	1 (6.7%)
5.05	n (%)	0 (0.0%)	1 (6.7%)
6.00	n (%)	10 (62.5%)	2 (13.3%)
6.02	n (%)	0 (0.0%)	1 (6.7%)

The compound of Formula (I) was slowly absorbed after oral administration in the fasted and fed conditions. In the fasted condition, the mean compound of Formula (I) C_{max} was approximately 53% lower than in the fed condition (731 vs. 1550 ng/mL). Due to a prolonged elimination phase, $t_{½}$ values and therefore, $AUC_{0-\infty}$ values could not be determined for some the compound of Formula (I) concentration-time profiles. Mean $AUC_{0-\infty}$ was approximately 47% lower in the fasted condition than in the fed condition (9440 vs. 17800 ng×hr/mL) for those subjects for whom $AUC_{0-\infty}$ could be determined. Mean $AUC_{0-tlast}$ was approximately 50% lower in the fasted condition than in the fed condition (8020 vs. 16200 ng×hr/mL). Median t_{max} was slightly longer in the fasted condition than in the fed condition (6.0 vs. 5.0 hours) and mean $t_{½}$ was shorter in the fasted condition than in the fed condition (33 vs. 42 hours) for those subjects for whom a $t_{½}$ could be determined. Variability in the compound of Formula (I) PK (geometric CV%) for AUC, C_{max}, $t_{½}$, and MRT was lower in the fed condition compared with the fasted condition.

The geometric mean ratios and associated 90% CIs for $AUC_{0-tlast}$ and C_{max} for the compound of Formula (I) after treatment with the compound of Formula (I) for the fed vs. fasted condition are provided in Table 21, below, where $AUC_{0-tlast}$= AUC from 0 hours to last measurable concentration, C_{max}=maximum plasma concentration, and PK=pharmacokinetic.

Table 21. Formula (I) geometric mean ratios for PK exposure parameters under fed vs. fasted conditions (safety analysis set)

Parameter	Ratio[a] (%) (Fed vs. Fasted Condition)	90% Confidence Interval[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	215.2	182.9, 253.1
C_{max} (ng/mL)	218.6	187.4, 255.1

[a] Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data.

[b] The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data.

The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0\text{-tlast}}$ for the fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0\text{-tlast}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Due to the missing $AUC_{0\text{-}\infty}$ values, the food effect on overall exposure was not assessed using $AUC_{0\text{-}\infty}$ values.

Conclusion

Administration of the compound of Formula (I) 50 mg under fed compared with fasted conditions resulted in a higher mean C_{max} of the compound of Formula (I) (approximately 2-fold higher; 1550 vs. 731 ng/mL), a longer $t_{½}$ (42 vs. 33 hours), a slightly shorter median t_{max} (5.0 vs. 6.0 hours), and a higher mean $AUC_{0\text{-}\infty}$ (approximately 2-fold higher; 17800 vs. 9440 ng×hr/mL). The compound of Formula (I) geometric mean ratios for C_{max} and $AUC_{0\text{-tlast}}$ for fed vs. fasted conditions were 218.6% and 215.2%, respectively, indicating that the compound of Formula (I) absorption was approximately 2-fold greater when administered with food. The upper and lower 90% CI bounds for both C_{max} (187.4%, 255.1%) and $AUC_{0\text{-tlast}}$ (182.9%, 253.1%) were outside of the "no-effect" range of 80.00% to 125.00%, indicating that there was a food effect on the compound of Formula (I) exposure. Similar results were observed with the hydroxylated metabolite of the compound of Formula (I). Overall, these results indicate that the compound of Formula (I) 50 mg was well tolerated in healthy subjects when administered under fasted or fed conditions and that the total AUC and C_{max} were increased when the compound of Formula (I) was taken with food.

Example 7: Phase 1 study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of formulations of the compound of Formula (I) in healthy adult subjects

A Phase 1 study to compare the relative bioavailability of a 50 mg dose of different formulations of the compound of Formula (I) as well as to evaluate the effect of fasting and fed conditions on the pharmacokinetics (PK) of the compound of Formula (I) was designed. The 50 mg dose was chosen for this study because it is within the tested dose range in completed Phase 1 and Phase 2 trials and was well tolerated in those studies. The objectives of the study are: to evaluate the PK and compare the relative bioavailability of the compound of Formula (I) 50 mg formulations in healthy adult subjects; to evaluate the effect of food on the PK of the compound of Formula (I) 50 mg formulations; and to evaluate the safety and tolerability of the compound of Formula (I) 50 mg formulations.

Study Design

This is a Phase 1, open-label, randomized, three-period crossover study of the relative bioavailability and the effect of food on the PK of the compound of Formula (I) 50 mg in healthy adult subjects. During treatment period 1 and treatment period 2, subjects will receive a single dose of the compound of Formula (I) 50 mg administered as an encapsulated, lipidic semi-solid (reference) and 1 of 2 different spray-dried dispersion (SDD) test formulations (suspension or capsule) under fed conditions, and during treatment period, three subjects will receive the same SDD test formulation under fasted conditions.

A total of 36 healthy adult subjects will be randomized to 1 of 4 treatment sequences (9 subjects per sequence; approximately equal distribution of males and females per sequence; see Table 22, below). There will be 21 days between each dose.

Table 22. Treatment sequences

Treatment sequence	Treatment period 1 (Fed)	Treatment period 2 (Fed)	Treatment period 3 (Fasted)
1	Reference	SDD suspension	SDD suspension
2	SDD suspension	Reference	SDD suspension
3	Reference	SDD capsule	SDD capsule
4	SDD capsule	Reference	SDD capsule

After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days prior to Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1, and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During treatment periods 1 and 2, subjects will fast overnight for at least 10 hours and then ingest a liquid dietary supplement (vanilla-flavored Ensure Plus®, 237 mL container) with the study drug and not consume any other food for 4 hours after dosing. During treatment period 3, subjects will fast overnight for at least 10 hours prior to dosing and continue to fast for an additional 4 hours after dosing. During all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water/liquid dietary supplement provided for study drug dosing.

On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 50 mg and have blood samples collected for PK analysis. Subjects will complete a taste satisfaction questionnaire after study drug ingestion on Day 1 of treatment period 3 (only for subjects who receive the SDD suspension under the fasted condition). Subjects will remain in the unit on the day of dosing and will be discharged on Day 2 of each treatment period, following completion of all required procedures, including collection of the 36-hour PK sample. On the mornings of Days 8 and 15 of each treatment period, subjects will return to the clinical unit on an outpatient basis for PK blood sample collection and safety assessments. On Day 21 of treatment period 1 and treatment period 2, subjects will arrive at the site and have Day 21 assessments completed, and they will stay overnight at the site and begin Day 1 of treatment period 2 or treatment period 3 the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 3 (21 ± 2 days after treatment period 3 dosing) or upon early termination.

Blood samples for PK analysis and safety assessments will be collected/conducted at scheduled times throughout the study. The study design schematic is shown in FIG. 10.

Duration of treatment

The expected duration of study participation for each healthy adult subject will be approximately 13 weeks, including up to 28 days of screening, 3 doses each separated by 21 days, and a final follow-up study visit 21 days after receiving the last dose of study drug during treatment period 3.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as two different test formulations for oral administration: as powder in bottles for constitution into a suspension (20 mL) and as

powder-filled capsules. The compound of Formula (I) test formulations will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow the study drug with a liquid dietary supplement (Ensure Plus® [237 mL container]) with an additional 100 mL of water (SDD capsule formulation) or with an additional 80 mL of water (SDD suspension formulation) during treatment period 1 or 2. Subjects must swallow the study drug with 330 mL of water (SDD capsule formulation) or 310 mL of water (SDD suspension formulation) during treatment period 3.

Reference therapy, dose, and mode of administration

The compound of Formula (I) reference formulation (encapsulated, lipidic semi-solid formulation) will be supplied as capsules for oral administration. The compound of Formula (I) reference capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. Subjects must swallow a single capsule with a liquid dietary supplement (Ensure Plus [237 mL container]) with an additional 100 mL of water during treatment period 1 or 2.

Criteria for Evaluation

Pharmacokinetics

Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to the time of the last measurable concentration ($AUC_{0\text{-}tlast}$)
- Area under the plasma concentration curve extrapolated from 0 hours to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)

- Molar AUC ratio of primary metabolite(s) to the parent drug the compound of Formula (I)

The following plasma PK parameters will be calculated only for the compound of Formula (I):

- Apparent systemic clearance after oral administration (CL/F)
- Apparent volume of distribution during terminal phase after oral administration (Vz/F)

Other assessment

A taste satisfaction questionnaire will be administered.

Safety assessments

Safety will be monitored throughout the study and will include the following assessments:

- AEs
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiogram (ECG)

Statistical methods

Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by formulation using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test formulation (SDD suspension and SDD capsule) vs. the reference formulation for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites under fed conditions. Further, two-sided 90% confidence intervals will be calculated for the ratio of each test formulation under fasted conditions vs. under fed conditions for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites.

Safety and taste satisfaction questionnaire data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

Pharmacokinetic results are shown in Tables 23-26, below.

Table 23: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Suspension Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Suspension (Fed) (N=18)**	**SDD Suspension (Fasted) (N=18)**
$AUC_{0\text{-tlast}}$ (ng×hr/mL)			
Mean (SD)	16600 (7880)	5980 (3960)	737 (417)
Geom CV(%)	46.8	72.8	68.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)			
Mean	17400 (8010)	6500 (4180)	893 (480)
Geom CV(%)	45.4	71.7	60.1
C_{max} (ng/mL)			
Mean (SD)	1480 (506)	672 (323)	72.3 (44.9)
Geom CV(%)	32.1	57.9	57.5
t_{max} (hr)			
Median (min,max)	5.0 (3.0, 6.0)	5.0 (5.0, 10)	7.0 (5.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.31)	0.85 (0.29)	1.2 (0.65)
$t_{½}$ (hr)			
Mean (SD)	50 (20)	19 (6.1)	9.0 (0.46)
Geom CV(%)	140	93	23
MRT (hr)			
Mean (SD)	36 (43)	23 (24)	17 (2.9)
Geom CV(%)	84	62	18
CL/F (L/hr)			
Mean (SD)	3.4 (1.4)	11 (8.0)	80 (54)
Geom CV(%)	45	72	63
Vz/F (L)			
Mean (SD)	180 (260)	210 (140)	970 (560)
Geom CV(%)	93	77	53
T_{last} (hr)			

Mean (SD)	170 (140)	77 (110)	31 (7.6)
Geom CV(%)	120	92	30

Table 24: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	32.2	(26.4%, 39.4%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	33.5	(27.7%, 40.6%)
C_{max} (ng/mL)	SDD Suspension (Fed) vs. Reference Capsule (Fed)	42.2	(34.8%, 51.2%)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.4	(3.4%, 5.7%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	5.0	(3.8%, 6.5%)
C_{max} (ng/mL)	SDD Suspension (Fasted) vs. Reference Capsule (Fed)	4.5	(3.8%, 5.4%)

Table 25: Summary of Plasma Pharmacokinetic Parameters (Safety Analysis Set – SDD Capsule Group)

		Compound of Formula (I) Plasma Concentration	
Parameter (units) Statistic	**Reference Capsule (Fed) (N=18)**	**SDD Capsule (Fed) (N=18)**	**SDD Capsule (Fasted) (N=17)**
$AUC_{0\text{-tlast}}$ (ng×hr/mL)			
Mean (SD)	19500 (7960)	9470 (4670)	1840 (1650)
Geom CV(%)	50.4	48.0	78.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)			
Mean	20100 (7850)	10000 (4610)	2120 (1830)
Geom CV(%)	47.1	44.9	73.7
C_{max} (ng/mL)			
Mean (SD)	1770 (494)	1110 (449)	143 (110)

Geom CV(%)	25.7	44.5	74.1
t_{max} (hr)			
Median (min,max)	5.0 (5.0, 8.0)	5.0 (3.0, 6.0)	7.0 (6.0, 12)
T_{lag} (hr)			
Mean (SD)	1.0 (0.38)	1.3 (0.49)	1.2 (0.88)
$t_{½}$ (hr)			
Mean (SD)	35 (18)	26 (20)	14 (11)
Geom CV(%)	69	98	49
MRT (hr)			
Mean (SD)	28 (12)	25 (14)	21 (9.2)
Geom CV(%)	45	55	31
CL/F (L/hr)			
Mean (SD)	3.0 (1.5)	5.9 (2.4)	36 (18)
Geom CV(%)	47	45	74
Vz/F (L)			
Mean (SD)	130 (61)	190 (140)	630 (380)
Geom CV(%)	47	75	72
T_{last} (hr)			
Mean (SD)	170 (96)	100 (89)	44 (32)
Geom CV(%)	91	100	39

Table 26: Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by formulation and fed vs fasted (Safety Analysis Set – SDD Suspension Group)

Analyte Parameter (units)	Treatment Comparison	Ratio (%)	90% CI
Compound of Formula (I)			
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	48.2	(41.4%, 56.1%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	49.7	(43.1%, 57.2%)
C_{max} (ng/mL)	SDD Capsule (Fed) vs. Reference Capsule (Fed)	59.8	(51.7%, 69.2%)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	8.0	(5.7%, 11.2%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	9.0	(6.6%, 12.4%)
C_{max} (ng/mL)	SDD Capsule (Fasted) vs. Reference Capsule (Fed)	6.7	(4.9%, 9.2%)

Example 8: Phase 2 study of the compound of Formula (I) in adult subjects with congenital adrenal hyperplasia

A Phase 2 study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of the compound of Formula (I) in adult subjects with classic congenital adrenal hyperplasia (CAH) was designed. The objectives of the study are: to assess the safety and tolerability of two ascending doses of the compound of Formula (I) in adult subjects with CAH; to evaluate the effect of repeated doses of the compound of Formula (I) on endogenous levels of PD biomarkers in adult subjects with CAH; and to evaluate plasma exposures following repeated doses of the compound of Formula (I) administered nightly.

The lower dose strength selected for this study, the compound of Formula (I) 50 mg, was well tolerated in both single and repeat-dose safety and PK studies in healthy volunteers. Doses up to 100 mg were also well tolerated in both single-dose and repeat-dose Phase 1 studies in healthy volunteers, and importantly, in a large Phase 2 study in non-elderly female and male subjects with major depressive disorder receiving the compound of Formula (I) during an 8-week, double-blind treatment period. Furthermore, the anticipated steady state exposures with the selected the compound of Formula (I) doses, using the predicted C_{max} and AUC, are within the acceptable safety margins defined by the nonclinical toxicology studies that have been conducted to date.

Study Design

A Phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, PK, and PD of the compound of Formula (I) in approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH was designed. The study will include a sequential-cohort design with four compound of Formula (I) dose cohorts: 50 mg and 100 mg, with each dose administered for 14 consecutive days:

- Cohort 1: compound of Formula (I) 50 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 2: compound of Formula (I) 100 mg once daily with a bottle of vanilla-flavored Ensure Plus® (~237 mL) at approximately 2200 hours.
- Cohort 3: compound of Formula (I) 100 mg once daily with the evening meal at approximately 1900 hours.
- Cohort 4: compound of Formula (I) 100 mg twice daily with breakfast at approximately 0700 hours and with the evening meal at approximately 1900 hours.

There will be an approximate 2-week period to evaluate safety and tolerability data before proceeding from Cohort 1 to Cohort 2. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects). Table 27 below depicts the dose cohorts, doses, and number of subjects per cohort.

Table 27. Dose cohorts, doses, and number of subjects

Cohort	Compound of Formula (I) Dose	Approximate Dosing Time(s)	Number of Subjects
1	50 mg	2200 hours	8-10
2	100 mg	2200 hours	8-10
3	100 mg	1900 hours	8-10
4	100 mg	0700 and 1900 hours	Up to 8

Subjects will be screened for eligibility to participate in the study for up to approximately 3 weeks (Days -28 to -8). Subjects who reenroll and have had a stable medication regimen for CAH since their last visit in this study do not have to undergo screening; those who reenroll and have had a change to their medication regimen for CAH must undergo a second screening visit. During screening, subjects will provide a single blood

sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

Eligible subjects who have a screening 17-OHP level ≥1,000 ng/dL will be admitted to the study center for 1 night and have baseline serial PD samples collected over a 24-hour period beginning in the evening of Day -7. Baseline serial PD samples will be collected at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects within each dose cohort will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for CYP21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (the compound of Formula (I) 50 or 100 mg) will be administered at approximately 2200 hours for Cohorts 1 and 2 and at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours for Cohorts 3 and 4. The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects in Cohorts 1 and 2 will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for cytochrome P450 (CYP) 21A2 genotyping. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. Study drug (compound of Formula(I) 50 mg or 100 mg) will be administered at approximately 2200 hours. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 12-hour post-dose PK/PD samples are collected (at approximately 1000 hours) on Day 2 and after the 16-hour post-dose PK/PD samples are collected (at approximately 1400 hours) on Day 15. Subjects will be discharged from the study center the evening on Days 2 and 15 following completion of all study-related procedures for those days. Prior to this discharge on Day 2, study drug will be administered at the study center at approximately 2200 hours. Study drug will then be self-administered nightly at home at approximately 2200 hours on Days 3 to 13. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 3 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

Subjects in Cohorts 3 and 4 will have a blood sample collected on Day 1 for CYP21A2 genotyping (only for subjects who have not previously participated in Cohorts 1 or 2). Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. For Cohort 3, study drug (compound of Formula(I) 100 mg) will be administered at home on Days 1 to 13 at approximately 1900 hours with each subject's evening meal. For Cohort 4, study drug compound of Formula(I) 100 mg) will be administered at home on Days 2 to 14 at approximately 0700 hours with each subject's breakfast and on Days 1 to 13 at approximately 1900 hours with each subjects' evening meal. For both cohorts, the Day 14 evening dose will be administered at the study site. Subjects will take their usual morning dose of concurrent steroidal treatments at approximately 1000 hours on Days 1 to 14. On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center. Subjects will be admitted to the study center on Day 14 (last day of dosing). On Day 14, subjects will receive study drug in the study center at approximately 1900 hours with a standard (moderate fat/moderate calorie) evening meal. The subjects' usual morning dose of concurrent steroidal treatments will be administered after PK/PD samples are collected at approximately 1400 hours on Day 15. Subjects will be discharged from the study center the evening on Day 15 following completion of all study-related procedures.

For all cohorts, follow-up visits on Days 21, 28, and 35 will be conducted at the study center or the subject's home by a qualified home healthcare provider (based on the subject's preference). A final study visit will be conducted at the study site approximately 5 weeks after the last dose of study drug (on Day 49 or early termination). There will be a visit window of -8 hours for Day 7, -8 hours/+3 days for Days 21, 28, and 35, and +7 days for the final study visit. Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study. The study design schematic is shown in FIG. 11.

Dose escalation procedure

Cohort 1 will consist of approximately 8 to 10 subjects who will receive a daily dose of the compound of Formula (I) 50 mg at approximately 2200 hours for 14 days (subjects will receive study drug at the site on Days 1, 2, and 14, and self-administer study drug at home on Days 3 to 13). Following the completion of Day 15 assessments for all subjects in the Cohort 1, a medical monitor will review the accumulated safety and tolerability results to ensure there are no safety concerns with proceeding to the 100 mg dose (Cohorts 2 and 3), and to determine if a maximum tolerated dose (MTD) has been reached. If the MTD is reached, no

dose escalation will occur. There will be an approximate 2-week period between Cohorts 1 and 2 to accommodate this safety review. A similar procedure will be used prior to proceeding to the 100 mg twice daily dose (Cohort 4).

If the medical monitor determines that it is safe to proceed to the compound of Formula (I) 100 mg, subjects in Cohort 2 will be administered the compound of Formula (I) 100 mg daily for 14 days. Dosing for Cohorts 3 and 4 may begin simultaneously with Cohort 2.

During the 14-day dosing period for any cohort, dosing may be postponed or halted if one or more subjects experience a severe or serious adverse event (AE), or if the type, frequency, or severity of AEs becomes unacceptable. If dosing is postponed, the medical monitor will review all available safety, tolerability, and PK data before allowing any further subjects to receive study drug.

Study Population

Approximately 30 adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled. Subjects who previously completed the current study in Cohort 1 or Cohort 2 may reenroll to participate in Cohorts 3 or 4 (in addition to new subjects).

Duration of treatment

The expected duration of study participation for each subject is approximately 11 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 5 weeks. The total duration of the study will be an additional 8 to 11 weeks for subjects who reenroll.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules containing 50 mg of the compound of Formula (I) free base for oral administration (see, e.g., Reference 1 formulation as described in Example 9). Doses of the compound of Formula (I) are 50 mg and 100 mg, administered in oral capsule form. Each dose of study drug for Cohorts 1 and 2 is to be administered with a bottle of vanilla-flavored Ensure Plus® (~237 mL). Each dose of study drug for Cohort 3 is to be administered with each subject's evening meal at approximately 1900 hours. Each dose of study drug for Cohort 4 is to be administered with each subject's breakfast at approximately 1900 hours (i.e., a total daily dose of 200 mg).

Criteria for Evaluation

Cohorts 1 and 2

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 2145, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 1 to 2 and Days 14 to 15 at: 15 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose; Day 7 (at approximately 24 hours post-dose); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours post-dose); and at the final study visit (Day 49 or early termination).

Cohorts 3 and 4

Blood samples to evaluate 24-hour PD baseline will be collected on Days -7 to -6 at approximately 1845, 2000, 2100, 2200, 2300, 2400, 0100, 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1800, 1900, and 2200 hours. Blood samples to evaluate PK and PD parameters of the compound of Formula (I) will be collected on Days 14 to 15 at the following times (for Cohort 4, all times are relative to evening dosing unless otherwise indicated): 15 minutes predose and at 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 17, 19, 23, 24, and 27 hours postdose; Day 7 (at 24 hours postdose for Cohort 3 or at 12 hours post morning dose but prior to the evening dose for Cohort 4); Days 21, 28, and 35 (at approximately 168, 336, and 504 hours postdose); and at the final study visit (Day 49 or early termination).

Pharmacokinetics

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-tlast}}$)
- Area under the plasma concentration versus time curve from 0 to 24 hours ($AUC_{0\text{-}24}$)
- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)

- Apparent mean residence time (MRT)

Additional PK parameters for Day 14 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (% fluctuation)
- Accumulation index at steady state
- Apparent systemic clearance after oral administration (CL/F) (the compound of Formula (I) only)

Pharmacodynamics

Primary: Morning 17-OHP (serum; ng/dL) from the 0600, 0800, and 1000 hour samples (8-, 10-, and 12-hour post-dose samples from Cohorts 1 and 2 and 11-, 13-, and 15-hour postdose samples from Cohorts 3 and 4.

Secondary: 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; µg/dL), and adrenocorticotropic hormone (plasma ACTH; pg/mL).

Safety

Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Adverse events
- Clinical laboratory tests - clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), hematology, coagulation (prothrombin time, aPTT, d-dimer, fibrinogen), and urinalysis (including quantitative myoglobin, casts and crystals)
- Vital signs
- Physical examinations (including musculoskeletal exam)
- 12-lead electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Brief Psychiatric Rating Scale (BPRS)

Statistical methods

Safety, PK, and PD variables will be summarized within each dose cohort (the compound of Formula (I) 50 mg and 100 mg) using descriptive statistics. Summaries of PD measures will include both observed values and changes from pre-dose.

Results

Pharmacokinetic results

Eight subjects (four female and four male) were enrolled in this study and completed Cohort 1. Age, sex, and BMI information for the study participants is shown in Table 28, below.

Table 28. Cohort 1 Subjects

Subject ID	Age (years)	Sex (Male/Female)	BMI (kg/m^2)
001	37	Female	24.9
002	25	Female	32.0
003	49	Male	37.2
004	36	Male	25.0
005	27	Female	25.5
006	19	Male	21.7
007	25	Male	27.5
008	31	Female	34.4

The subjects received a daily dose of the compound of Formula (I) at 50 mg at approximately 2200 hours (~10 p.m. or bedtime) for 14 days. Arithmetic mean values for ACTH (FIG. 12A) and 17-OHP (FIG. 12B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, Day 1, and Day 14. Both ACTH and 17OHP concentration profiles at day 1 and day 14 show clear reductions from the baseline mean profiles. Cohort 1 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) are shown in Table 29 below. These PK parameters are consistent with observations from Phase 1 studies in healthy volunteers.

Table 29. Cohort 1 Mean PK parameters of T_{max}, C_{max}, and AUC_{24}

	Day 1			Day 14		
	T_{max}	C_{max}	AUC_{24}	T_{max}	C_{max}	AUC_{24}
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24

Additional measurements of cohort 1 and cohort 2 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) on Day 1 of dosing are shown in Table 30 below.

Table 30: Mean PK parameters of T_{max}, C_{max}, and AUC_{24} on Day 1 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure		
Day 1	T_{max}* (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)	T_{max} (h)	C_{max} (ng/ml)	AUC_{24} (h*ng/ml)
G.Mean	6	1,270	10,411	4	2,370	24,725
CV%	-	25	24	-	21	42
N	8	8	8	8	4	4

*Median

Additional measurements of cohort 1, cohort 2 and cohort 3 mean PK parameters of T_{max}, C_{max}, and AUC_{24} for the compound of Formula (I) on Day 14 of dosing are shown in Table 31 below.

Table 31: Mean PK parameters of T_{max}, C_{max}, and AUC_{24} on Day 14 of dosing

	Cohort 1 50 mg- Ensure			Cohort 2 100 mg-Ensure			Cohort 3 100 mg w/evening Meal		
Day 14	Tmax* (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)	Tmax (h)	Cmax (ng/ml)	AUC24 (h*ng/ml)
G. Mean	4	1,335	14,070	4	3,379	35,416	3	3,650	34,706
CV%		15	24		31	37		32	15
N	8	8	8	6	6	6	8	8	8

*Median

Arithmetic mean values for androstenedione (FIG. 13A) and testosterone (FIG. 13B) for all 8 Cohort 1 subjects were plotted at each timepoint for Pre-treatment Baseline, day 1, and day 14. The androstenedione concentration profile on Day 1 and Day 14 shows a clear reduction from the baseline mean profile.

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of ACTH show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 14A). Arithmetic

mean values across all three timepoints show >=50% reductions from baseline at Day 1 and Day 14 (FIG. 14B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of 17-OHP show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 15A). Arithmetic mean values across all three timepoints show >=40% reductions from baseline at Day 1 and Day 14 (FIG 15B).

When focusing exclusively on the critical morning window period (timepoints at 8-, 10-, and 12-hours postdose) from 6:00 a.m. to 10:00 a.m., the levels of androstenedione show marked reductions from baseline at each of the 3 timepoints on Days 1 and 14 (FIG. 16A). Arithmetic mean values across all three timepoints show >=30% reductions from baseline at Day 1 and Day 14 (FIG. 16B).

A summary of reduction in 17-OHP and androstenedione in cohort 1 is shown in Table 32. Further, the androstenedione levels of three subjects was normalized by the treatment for the three subjects with Subject ID Nos. 001, 002, and 006).

Table 32. Cohort 1 Summary of Reduction in 17-OHP and Androstenedione at each timepoint in the morning window (6 a.m. to 10 a.m.)

Subject ID	Sex/ Age	Dosing Day	17-OHP % change from baseline			Androstenedione % change from baseline		
			6 AM	8 AM	10 AM	6 AM	8 AM	10 AM
001	F/37	D1 D14	-61.4 -90.3	14.7 -67.2	-24.1 -37.2	-42.0 -84.6	2.0 -58.6	-19.5 -55.1
002	F/25	D1 D14	-96.0 -37.7	-95.5 -58.6	45.4 -24.9	-68.0 -34.2	-66.7 -47.8	-21.7 -38.7
003	M/49	D1 D14	-11.8 -24.5	-46.6 -5.2	-34.0 -22.9	-13.4 -7.5	-47.1 -10.8	-22.7 -16.0
004	M/36	D1 D14	-13.7 -53.6	17.1 -46.8	10.1 -35.8	4.5 -13.8	15.9 -15.2	3.0 -21.2
005	F/27	D1 D14	-24.4 -78.8	-83.6 -95.1	-52.2 -86.3	-35.6 26.7	-50.3 -13.7	-33.5 -10.9
006	M/19	D1 D14	-5.1 -25.4	-1.1 -20.4	-97.8 -98.3	-10.0 -67.8	-18.5 -62.7	-78.9 -92.1
007	M/25	D1 D14	-50.0 14.9	-28.0 4.0	-27.4 -7.1	-24.8 -4.8	-30.0 -36.8	-15.8 -30.2
008	F/31	D1 D14	-64.5 -59.0	-80.7 -65.2	-92.8 -89.1	-12.2 74.5	7.0 99.4	-9.3 59.2

Table 33. Cohort 1 Summary of PK parameters of T_{max}, C_{max}, and AUC_{24} for each subject at days 1 and 14

	Day 1			Day 14		
Subject ID	**T_{max} (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**	**T_{max} (h)**	**C_{max} (ng/ml)**	**AUC_{24} (h*ng/ml)**
001	6	1830	14,487	6	1570	20,863
002	6	1210	11,829	4	1610	15,494
003	6	1060	11,068	3	1310	15,599
004	4	1670	9,669	3	1160	10,180
005	8	961	9,266	6	1550	15,130
006	4	1030	6,574	3	1090	10,288
007	6	1550	8,239	6	1170	12,880
008	3	1130	11,209	4	1330	13,944
Mean	**5.4**	**1305**	**10,292**	**4.4**	**1349**	**14,297**
CV%	30	25	24	32	15	24
N	8	8	8	8	8	8

After 14 days of once-daily compound of Formula (I) administration, a majority of participants in Cohorts 1-3 showed reduced serum concentrations of adrenal androgens and precursors. Mean changes from baseline (±standard deviation) in Cohort 1 were as follows: 17-OHP, -2341.0±1535.0 ng/dL; androstenedione, -98.4±98.7 ng/dL; and ACTH, -157.0±194.9 pg/mL. Mean reductions were larger in Cohort 2 (17-OHP, -4406.0±5516.1; androstenedione, -362.8±354.0; ACTH, -180.9±155.2) and Cohort 3 (17-OHP, -4760.1±4018.2; androstenedione, -210.9±188.6; ACTH, -358.9±177.6), suggesting a possible dose response. FIGs. 17A-17C, 18A-18C, and 19A-19C depict results from Cohorts 1, 2, and 3, respectively.

Summary

The results from this ongoing Phase II open-label study demonstrated a reduction of at least 50 percent from baseline in 17-hydroxyprogesterone (17-OHP) and adrenocorticotropic hormone (ACTH) levels in more than 50 percent of CAH patients in cohort 1 treated with the compound of Formula (I) for 14 days (i.e., 6 of 8 patients in cohort 1 had a reduction of ≥50% from baseline levels of 17-OHP during at least one morning window timepoint, see, e.g., Table 32). Meaningful reductions were also observed in other biomarkers, including androstenedione (i.e., 4 of these patients also had a reduction of ≥50% from baseline levels of androstenedione during at least one morning window timepoint, see, e.g., Table 32). The greater reductions in biomarkers in cohorts 2 and 3, treated with double the dose of the compound of Formula (I)

compared with cohort 1, suggest a possible dose response. Further, the compound of Formula (I) was well-tolerated with a relatively small number of mild adverse events (AEs) reported (e.g., headache, ovulation pain, fatigue, localized infection (toe), dizziness, nausea, URI, contusion with the most common being headache). No clinically significant findings from routine labs, vital signs, or electrocardiograms were found.

Example 9: Reference Formulation 1 of the compound of Formula (I)

Tables 34A and 34B show Reference formulation 1 of the compound of Formula (I) as used in the clinical studies described in Examples 6 and 8, above. An example manufacturing process is shown in FIG. 20. Another example manufacturing process is shown in FIG. 21.

Table 34A:

Component	**Quality Standard**	**Function**	**50 mg Capsule**	
			Weight (mg/unit)	**% (w/w)**
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (Labrafac TM Lipophile WL1349)	NF	Oily Phase Vehicle	196.0	39.2
Propylene Glycol Dicaprylate/Dicaprate, (LabrafacTM PG)	NF	Emulsifying Agent	102.0	20.4
Lauroyl Polyoxyl-32 Glycerides (Gelucire® 44/14)	NF	Nonionic Surfactant & Solubilizing Agent	95.0	19.0
Vitamin E Polyethylene Glycol Succinate (Kolliphor® TPGS)	USP/NF	Solubilizing Agent	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Gelatin Capsule Shell. Size #00, Swedish Orange cap/body; (Coni-Snap®)	Non Pharmacopocial	Capsule Shell	--	--

Gelatin Powder, 220 Bloom	USP	Capsule shell banding agent	--	--
Purified Water	USP	Capsule shell banding solvent	--	--

Table 34B:

Component	**Quality Standard**	**Function**	**50 mg Capsule**	
			Weight (mg/unit)	**% (w/w)**
Compound of Formula (I), free base	In-house	Active Ingredient	50.0	10.0
Medium-Chain Triglycerides (caprylic:capric acid 60:40; Miglyol 812N)	Ph. Eur./NF	Vehicle	195.85	39.2
Propylene Glycol Dicaprylocaprate, (LabrafacTM PG)	Ph. Eur.	Vehicle	102.15	20.4
Lauroyl macrogolglycerides type 1500-Lauroyl polyoxylglycerides type 1500 (Gelucire® 44/14)	Ph. Eur./NF	Surfactant	95.0	19.0
Vitamin E Polyethylene Glycol Succinate, 260 mg/g *d*-alpha tocopherol (Vitamin E/TPGS 260)	NF	Surfactant	57.0	11.4
Total Emulsion Weight			**500.0**	**100.0**
Orange opaque hard capsule, size 0, composed of gelatin, titanium dioxide and red ferric oxide (Swedish Orange ®)	Non Pharmacopoeial	Capsule Shell	--	--
Ethanol (96%) and Purified Water	USP	Capsule shell banding solvent	--	--

Example 10: Study Evaluating Effect of Ensure Plus, Ensure Pudding, Milk and High Fat Meal on Reference Capsule

Study design

This is a Phase 1, open-label, randomized, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the PK, safety, and tolerability of the compound of Formula (I) in healthy adult subjects.

A total of 16 healthy adult subjects (8 males and 8 females) will be randomly assigned to 1 of 4 treatment sequences (4 subjects per sequence [2 males and 2 females per sequence]; see Table 35 below). During each treatment period, subjects will receive a single dose of the compound of Formula (I) 100 mg administered with the appropriate meal, according to the randomization scheme. There will be a washout of at least 21 days between each dose.

Table 35:

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	Reference meal	Test meal 1	Test meal 2	Test meal 3
2	Test meal 1	Test meal 3	Reference meal	Test meal 2
3	Test meal 2	Reference meal	Test meal 3	Test meal 1
4	Test meal 3	Test meal 2	Test meal 1	Reference meal

Reference meal: vanilla-flavored Ensure Plus® Test meal 1: Low fat, low caloric content meal 1 Test meal 2: Low fat, low caloric content meal 2
Test meal 3: standard high fat, high caloric content meal

After providing informed consent, subjects will be screened for eligibility to participate in the study. Screening will begin up to 28 days before Day 1 of treatment period 1. Eligible subjects will be admitted to the clinical unit on Day -1 and randomized to 1 of the 4 treatment sequences on Day 1 of treatment period 1. During each treatment period, subjects will fast overnight for at least 10 hours until the start of the assigned meal, according to the randomization scheme, and ingest the study drug at approximately 0800 hours. Subjects must complete the entire meal within the specified time period and should not consume any other food for 4 hours after dosing. For all treatment periods, water will not be permitted for 1 hour before dosing until 2 hours after dosing except for the water provided with study drug dosing and planned meals.

On Day 1 of each treatment period, subjects will be dosed with the compound of Formula (I) 100 mg. Blood samples will be collected for PK analysis over a period of 36 hours during the in-house stay. During each treatment period, subjects will remain in the clinic on the day of dosing and will be discharged on Day 2 after completing all required procedures. On the mornings of Days 8 and 15 of each treatment period, subjects will return for an outpatient visit to the clinic for PK blood sample collection and safety assessments. On Day 21 of treatment periods 1 to 3, subjects will arrive at the site and have Day 21 assessments completed and they will stay overnight at the site and begin Day 1 of the subsequent treatment period the following day. A final follow-up study visit will be conducted on Day 22 of treatment period 4 (21 ± 2 days after treatment period 4 dosing) or upon early termination.

Blood samples for PK d/conducted at scheduled times throughout the study.

Study population

Sixteen healthy adult subjects (8 males and 8 females) between 18 and 55 years of age, inclusive, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment

The expected duration of study participation for each healthy adult subject will be approximately 16 weeks, including up to 28 days of screening, 4 days of dosing with at least 21 days between consecutive doses, and a final follow-up study visit 21 days (± 2 days) after receiving the last dose of study drug during treatment period 4.

Test product, dose, and mode of administration

The compound of Formula (I) will be supplied as capsules for oral administration (encapsulated, lipidic semi-solid formulation, e.g., Example 9). The compound of Formula (I) capsules will contain 50 mg of the compound of Formula (I) as free base equivalent. During each treatment period, subjects will receive two 50 mg capsules (100 mg) of the study drug along with a meal and water as defined by the randomization scheme. The food, water, and study drug administration are as follows:

Reference meal: Two capsules of study drug will be administered approximately 5 minutes after the start of a liquid dietary supplement (i.e., Ensure Plus® [237 mL container]) and an additional 120 mL of water for study drug dosing.

Test meal 1: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 1 with 120 mL of water for study drug dosing.

Test meal 2: Two capsules of study drug will be administered approximately 5 minutes after the start of a low fat, low caloric meal 2 with 120 mL of water for study drug dosing.

Test meal 3: Two capsules of study drug will be administered approximately 30 minutes after the start of a high fat, high caloric meal with 120 mL of water for study drug dosing.

CRITERIA FOR EVALUATION

Pharmacokinetics

Blood samples for assessment of plasma concentrations of the compound of Formula (I) and metabolites will be collected within 45 minutes before dosing, and at approximately 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 168, 336, and 504 hours after dosing.

The following plasma PK parameters will be calculated for the compound of Formula (I) and metabolites:

- Area under the plasma concentration versus time curve from 0 hours to last measurable concentration ($AUC_{0\text{-tlast}}$)
- Area under the plasma concentration versus time curve from 0 hours extrapolated to infinity ($AUC_{0\text{-}\infty}$)
- Maximum plasma concentration (C_{max})
- Time to achieve maximum plasma concentration (t_{max})
- Delay time between time of dosing and time of appearance of measurable test article (T_{lag})
- Apparent terminal half-life ($t_{½}$)
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)
- Molar AUC ratio of primary metabolite(s) to the parent drug compound of Formula (I). The following plasma PK parameters will be calculated only for the compound of Formula (I):
- Apparent systemic clearance after oral administration (CL/F)

- Apparent volume of distribution during terminal phase after oral administration (V_z/F)

Safety Assessments

Safety will be monitored throughout the study and will include the following assessments:

- Adverse events (AEs)
- Clinical laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis)
- Vital sign measurements (including orthostatic blood pressure and pulse rate)
- Physical examinations
- 12-lead electrocardiograms (ECGs)

Statistical methods

Pharmacokinetic parameters will be calculated using noncompartmental methods and summarized by meal type (test meal/reference meal) using descriptive statistics. Two-sided 90% confidence intervals will be calculated for the ratio of each test meal versus the reference meal for $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} for the compound of Formula (I) and metabolites. Safety data will be summarized with descriptive statistics.

Results

Pharmacokinetic results

Pharmacokinetic results are shown in Table 36 below.

Table 36: Summary of Plasma Pharmacokinetic Parameters

		Compound of Formula (I) Plasma Concentration		
Parameter (units) Statistic	**Ensure Plus (Fed) (N=18)**	**Ensure Pudding (Fed) (N=18)**	**Whole Milk (Fed) (N=17)**	**High Fat Meal (Fed) (N=17)**
$AUC_{0-tlast}$ (ng×hr/mL)				
Mean (SD)	36703 (17400)	34077 (11597)	35561 (15866)	55487 (23242)
Geom CV(%)	58	39.7	44.6	41.9

$AUC_{0-\infty}$ (ng×hr/mL)				
Mean	45386 (19648)	40037 (9515)	46737 (17395)	63755 (19139)
Geom CV(%)	43.3	23.8	38.8	31
C_{max} (ng/mL)				
Mean (SD)	3090 (1070)	3038 (984)	2835 (1005)	4336 (1938)
Geom CV(%)	39.7	34.9	34.5	53.6
t_{max} (hr)				
Median (min,max)	5.0 (2.0, 10.0)	5.0 (4.0, 6.0)	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
T_{lag} (hr)				
Mean (SD)	0.38 (0.46)	0.20 (0.25)	0.16 (0.31)	0.29 (0.37)
$t_{½}$ (hr)				
Mean (SD)	361 (263)	373 (196)	373 (143)	326 (120)
Geom CV(%)	61.1	48.6	37.1	33.8
CL/F (L/hr)				
Mean (SD)	2.49 (0.956)	2.636 (0.659)	2.427 (0.975)	1.706 (0.526)
Geom CV(%)	41.2	24.8	38.8	31.1
Vz/F (L)				
Mean (SD)	1254 (906)	1414 (720)	1308 (627)	816 (378)
Geom CV(%)	72.7	58.4	61.3	54.9

Example 11: Spray-dried Dispersion Granule Formulation of the Compound of Formula (I) (SDD-G)

Table 37 shows a granule formulation of the compound of Formula (I) using a SDD prepared according to Example 3, above. An example manufacturing process is shown in FIG. 22A and FIG. 22B.

Table 37:

Component	Quality Standard	Function	50 mg Sachet		Batch Weight (g)
			Weight (mg/unit)	% (w/w)	
Example 3, SDD	In-house	Drug Substance	200.0	13.33	40
Calcium Silicate (ZEOPHARM 250)	NF	Glidant	10.0	0.67	2
Mannitol (Pearlitol 200SD)	NF / EP / JP	Filler	832.5	55.5	166.5
Microcrystalline Cellulose (Avicel PH-102)	NF / EP / JP	Filler	300.0	20.0	60
Croscarmellose Sodium (Ac-Di-Sol®) SD711	NF / EP / JP	Disintegrant	150.0	10.0	30
Sodium Stearyl Fumarate	NF / EP / JP	Lubricant	7.5	0.5	1.5
Total			1500	100.0	300

Example 12: Liquid Formulation 1 of the Compound of Formula (I)

Table 38 shows liquid formulation 1 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 23.

Table 38:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.03
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.69
FONA orange flavor	NF	Flavor	1.0	0.1	0.41
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	94.58	358.87
Total			1 mL	100.0	380.6

Example 13: Liquid Formulation 2 of the Compound of Formula (I)

Table 39 shows liquid formulation 2 of the Compound of Formula (I) free base. An example manufacturing process is shown in FIG. 24.

Table 39:

Component	Quality Standard	Function	50 mg/mL Oral Solution		Batch Weight (g)
			Weight (mg/mL)	% (w/v)	
Compound of Formula (I) FB	In-house	Drug Substance	50.0	5	20.17
Saccharin	NF / EP	Sweetener	1.5	0.15	0.61
Butylated hydroxytoluene	NF / EP	Anti-oxidant	1.7	0.17	0.68
LABRAFIL M 1944 CS	NF / EP	Surfactant	200.0	20	80.16
FONA orange flavor	NF	Flavor	1.0	0.1	0.40
Labrafac Lipophile WL1349	NF / EP	Liquid Vehicle	to 1 mL	74.58	278.68
Total			1 mL	100.0	380.7

Example 14: A Phase I, Open-Label Study to Evaluate the Pharmacokinetics, Relative Bioavailability, Effect of Food, Safety and Tolerability of Different Compound of Formula (I) Prototype Formulations in Healthy Adult Subjects.

Methodology

This is a single center, open-label, randomized, single dose 4-period crossover study in healthy adult subjects designed to investigate the pharmacokinetic (PK) and safety of up to 4 compound of Formula (I) liquid lipidic prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulations, 50 mg/mL), a compound of Formula (I) spray dried dispersion formulation (compound of Formula (I) Granule for Sprinkle, 25 – 50 mg) and compound of Formula (I), 50 mg Capsules (Reference). It is planned to enroll 36 subjects to be allocated as 3 cohorts of 12 subjects per cohort, with 6 sub-cohorts of 6 subjects per sub-cohort. In each of these 6 sub- cohorts, 6 subjects will be assigned to one of 3 sub-cohorts where a single oral dose of Investigational Medicinal Product (IMP) is administered in 4 dosing periods (Periods 1 to 4) in multiple fed or fasted states or to one of 3 sub-cohorts where a single oral dose of IMP is administered in 2 dosing periods (Periods 1 and 2) only in

the fed state. Within each sub-cohort, subjects will also be randomized before administration of the first dose of IMP in Period 1 to one of the following treatment sequences (Table 40):

Table 40:

Sub-Cohort	Sequence	Number of Subjects	Total Number of Periods Dosed	Regimen			
				Period 1	Period 2	Period 3	Period 4
1A	ABEF	3	4	Regimen A	Regimen B	Regimen E	Regimen F
	BAEF	3	4	Regimen B	Regimen A	Regimen E	Regimen F
1B	AB	3	2	Regimen A	Regimen B	N/A	N/A
	BA	3	2	Regimen B	Regimen A	N/A	N/A
2A	ADEF	3	4	Regimen A	Regimen D	Regimen E	Regimen F
	DAEF	3	4	Regimen D	Regimen A	Regimen E	Regimen F
2B	AD	3	2	Regimen A	Regimen D	N/A	N/A
	DA	3	2	Regimen D	Regimen A	N/A	N/A
3A	ACEF	3	4	Regimen A	Regimen C	Regimen E	Regimen F
	CAEF	3	4	Regimen C	Regimen A	Regimen E	Regimen F
3B	AC	3	2	Regimen A	Regimen C	N/A	N/A
	CA	3	2	Regimen C	Regimen A	N/A	N/A

At informed consent, subjects will agree either to participate in 2 study periods or 4 study periods. Once placed into a sub-cohort, the order in which subjects receive the study treatments will be randomized based on the schedule above.

Subjects will receive up to 4 regimens in up to 4 periods in an order according to the randomization schedule within each sub-cohort.

The effect of different prandial states on the PK of the compound of Formula (I) may be explored in Periods 3 and 4 by administering in the fasted state or after an alternative meal (e.g. high fat, standard or light breakfast, etc.).

The proposed regimens are presented in Table 41 below:

Table 41:

Regimen	Investigational Medicinal Product	Dose	Route of Administration	Prandial State
A	Compound of Formula (I), 50 mg Capsules (Reference)	50 mg	Oral	Fed (Ensure Plus)
B	Compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
C	Compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL	50 mg	Oral	Fed (Ensure Plus)
D	Compound of Formula (I) Granule for Sprinkle, 25 – 50 mg	50 mg	Oral	Fed (Ensure Plus)
E	Compound of Formula (I) Oral Solution, Prototype Formulation 1	100 mg	Oral	Fed (Ensure Plus)
F	Compound of Formula (I) Oral Solution, Granule for Sprinkle	50 mg	Oral	Fed (alternative meal)

Study Design:

Subjects will be screened for eligibility to participate in the study up to 28 days before the first dose of IMP in Period 1. Each study period will follow the same study design. Subjects will be admitted to the clinical unit on the evening prior to IMP administration (Day -1). For Periods 1 and 2 (Regimen A and one of either Regimens B, C or D), all subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement (Ensure Plus). For Periods 3 and 4 (Regimens E and F), subjects will receive the compound of Formula (I) formulations in the morning according to the randomization schedule in the fed state with a liquid dietary supplement or an alternate prandial state (fasted or alternative meal). IMP administration will be performed on Day 1 with an appropriate interval between subjects based on logistical requirements (approximately 10 min). Meals will be standardized for each treatment regimen across periods.

Subjects will remain in the clinical unit until 36 h post-dose when they will be discharged. Subjects will return to the clinical unit at 168 h (7 days) and 336 h (14 days) post-dose for a PK blood sample and safety assessments. The minimum washout between IMP

dosing occasions will be 14 days between Periods 1 and 2 and 21 days or more to accommodate interim data reviews between Periods 2 and 3 and between Periods 3 and 4.

There will be a follow-up phone call 18 to 24 days post-final visit to ensure the ongoing wellbeing of subjects.

Following the completion of Period 2 for all cohorts, there will be an interim data review during which the PK and safety data will be reviewed, plus any relevant emerging Chemistry, Manufacturing and Control (CMC) stability study information, to determine the formulation, dose level and prandial state in which to administer the IMP in Period 3 (Regimen E). There will be a similar interim review following completion of Period 3 (administration of Regimen E) to determine the formulation, dose level and prandial state in which to administer the IMP in Period 4 (Regimen F). The criteria for the interim decisions will be based on available compound of Formula (I) PK data: e.g., C_{max}, T_{max}, AUC(0-36), F_{rel} and safety data.

Number of Subjects Planned:

It is planned to enroll 36 healthy male and female (non-pregnant, non-lactating) subjects in 6 sub-cohorts of 6 subjects per sub-cohort. These sub-cohorts will be combined in sets of 2 to create 3 cohorts of n = 12 for Periods 1 and 2 to target data in 10 evaluable subjects in each cohort for the primary objectives per formulation variant. A total of 18 subjects, 6 from each of Sub-Cohorts 1A, 2A and 3A participating in Periods 1 and 2, will additionally participate in Periods 3 and 4 with a target of a minimum of 6 evaluable subjects. A subject will be considered evaluable for a particular regimen if they have received an IMP and has completed sufficient planned PK assessments up to 336 h (14 days) after dosing for that regimen to allow for the assessment of study endpoints. A subject will be considered evaluable for a particular comparison (e.g., food effect, relative bioavailability) if they have received both IMPs under comparison and have sufficient PK data up to 14 days after each regimen to allow for assessment of study endpoints.

Subjects withdrawn due to an IMP-related adverse event (AE) will not be replaced. Subjects who are withdrawn for other reasons may be replaced as required by agreement between the principal investigator (PI) and sponsor to ensure sufficient numbers of evaluable subjects at the end of each study period. Replacement subjects may be required to be dosed with specific formulations from the previous regimens in order to obtain the minimum number of evaluable subjects required for interim decisions and to obtain data in any other regimen that is required to fulfil the study objective comparisons, with the exception that any

previously dosed IMP that has been considered sub-optimal will not be dosed. Up to 8 replacement subjects in total may be enrolled into the study. The maximum number of subjects that may be dosed is 44 in total.

If a subject withdraws from Sub-Cohort 1A, 2A or 3A after Period 2, it is acceptable to replace them with a subject from Sub-Cohort 1B, 2B or 3B provided the subject signs an updated consent form agreeing to participate in four treatment periods. At the discretion of the investigator, such a subject may not be required to undergo repeat screening procedures.

Duration of Study:

For subjects enrolled to receive single dose administration on 4 separate occasions in Periods 1 to 4 (Sub-Cohorts 1A, 2A and 3A), the estimated time from screening until the follow-up phone call is approximately 15 to 16 weeks.

For subjects enrolled to receive single dose administration on 2 separate occasions in Periods 1 to 2 only (Sub-Cohorts 1B, 2B and 3B), the estimated time from screening until the follow-up phone call is approximately 8 to 9 weeks.

Pharmacokinetic Assessments:

The plasma concentration data for a compound of Formula (I) will be analyzed for final reporting by Quotient Sciences and for interim reviews by Neurocrine Biosciences, Inc. (NBI), using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA). NBI will be responsible for PK analysis for interim review.

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters (Table 42) where possible and appropriate:

Table 42:

T_{lag}	Time prior to the first measurable (non-zero) concentration
T_{max}	Time to maximum plasma concentration
C_{max}	Maximum plasma concentration
$AUC_{0\text{-}tlast}$	Area under the plasma concentration versus time curve (AUC) from 0 h to last measurable concentration

AUC_{0-inf}	AUC from 0 h extrapolated to infinity
AUC_{extrap}	Percentage of AUC_{0-inf} extrapolated beyond the last measurable concentration
Lambda-z	Slope of the apparent terminal phase
$T_{1/2}$	Apparent terminal half-life
CL/F^a	Apparent systemic clearance after oral administration
Vd/F^a	Apparent volume of distribution based on the area after a single oral administration
MRT	Mean residence time
MPR $AUC_{0-tlast}$	Metabolite to parent ratio based on $AUC_{0-tlast}$
MPR AUC_{0-inf}	Metabolite to parent ratio based on AUC_{0-inf}

Taste Assessments:

Taste will be assessed for each IMP formulation and vehicle (e.g., Ensure Plus, soft food) using a questionnaire designed for this purpose and adapted for this specific study as required.

The questionnaire will ask subjects to rate the acceptability of smell, sweetness, bitterness, flavor, mouth feel, and aftertaste on a 6-point scale, and overall experience on a 5-point scale for each IMP formulation independently of any previous formulations.

Statistical Methodology:

Descriptive summaries for all safety data, PK assessments and taste questionnaire data will be provided. No hypothesis testing will be performed for the safety or taste questionnaire data.

Periods 1 and 2 – for Each Cohort Separately

Relative Bioavailability

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability (Frel) using a mixed effects model with terms for regimen, period and

sequence as fixed effects and subject within sequence as a random effect. Ratios of geometric means (GMRs) and 90% confidence interval (CI) for the relevant comparison of interest, i.e., between each of the prototype formulations (compound of Formula (I) Oral Solution, Prototype Formulation 1, 50 mg/mL, e.g., Example 12; compound of Formula (I) Oral Solution, Prototype Formulation 2, 50 mg/mL, e.g., Example 13; and compound of Formula (I) Granule for Sprinkle, 25 – 50 mg, e.g. Example 11 [Regimens B, C and D, respectively]) and compound of Formula (I), 50 mg Capsules, e.g., Example 9 (Reference; Regimen A) will be presented.

All Periods (Periods 1 to 4)

Food Effect

Statistical modelling will be performed on the compound of Formula (I) PK parameters AUC(0-tlast), AUC(0-inf) and Cmax to assess for the effects of food, if relevant. The natural log-transformed PK parameters will be analyzed for bioavailability using a mixed effects model with terms for prandial state (and meal type if applicable) as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparisons of interest will be presented where the ratio is defined as fasted/fed or test meal/reference meal (if applicable).

Relative Bioavailability

Statistical modelling will be performed on the natural log-transformed compound of Formula (I) PK parameters (AUC(0-tlast), AUC(0-inf) and Cmax) to assess relative bioavailability using a mixed effects model with terms for regimen as a fixed effect and subject as a random effect. Ratios of geometric means and 90% CI for the relevant comparison of interest i.e., between each of the prototype formulations (Regimens E and F, IMPs to be determined by interim reviews following completion of Periods 2 and 3) and compound of Formula (I), 50 mg Capsules (Reference; Regimen A) will be presented.

Results

Preliminary PK data is summarized in Table 43 below:

Table 43: Preliminary Data from Periods 1 and 2

	A- Reference	B-Oral Solution 1	C-Oral Solution 2	D- SDD Granule
N	35	12	12	12
Tmax * (h)	5 (2,6)	6 (5,7)	5 (5,7)	5 (5,7)
Cmax (ng/ml)	1361 (33)	790 (31)	1082 (46)	1075 (35)
AUC36 (h*ng/ml)	9452 (30)	5556 (34)	7582 (37)	6691 (41)

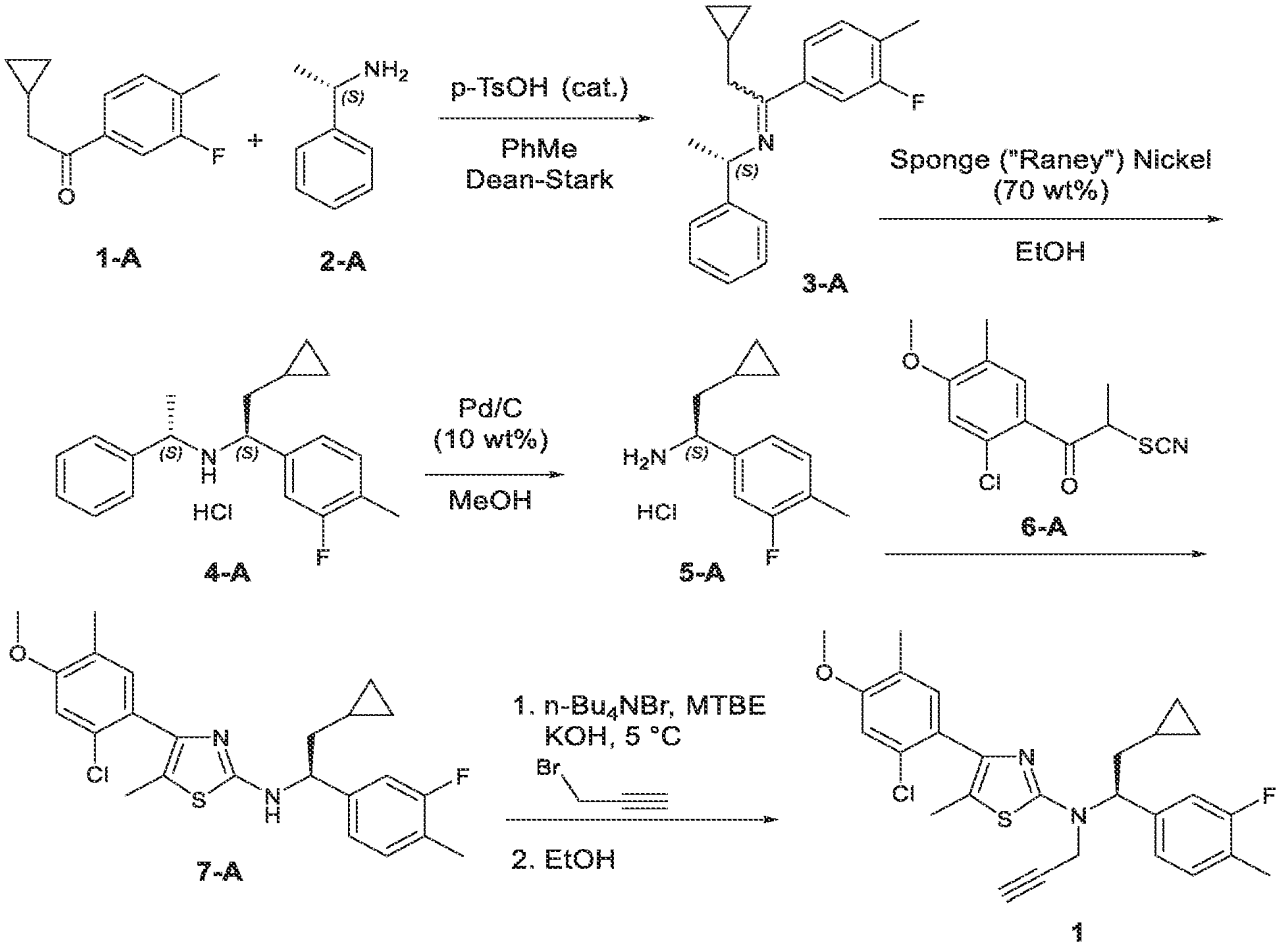
*Geometric Mean /CV% for AUC and Cmax; Median for Tmax

Example 15. Compound of Formula (I) Crystalline Free Base Form I

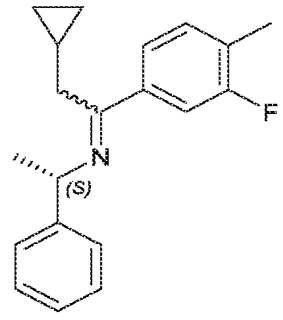
Example 15A

Scheme 1: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), Form I)

Scheme 1



Step 1: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-(1-phenylethyl)ethan-1-imine (Compound 3-A)

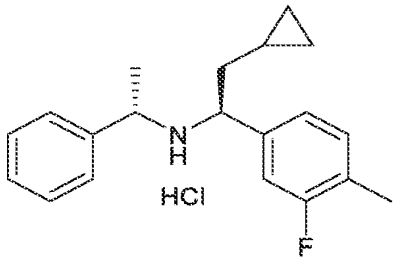


Compound 3-A

A mixture of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (1-A, 150.7 kg, 1 eq., as a 27.6% w/w solution in toluene, Example 15C), (*S*)-(−)-1-Phenylethylamine (2-A, 112.9 kg, 1.19 eq.), and *p*-toluenesulfonic acid (7.4 kg, 0.05 eq.) is refluxed at 110 – 120 °C for 23 – 25 h in a reactor set up in a Dean-Stark configuration. The solvent is then removed

at 125 – 135 °C under atmospheric pressure until distillation halts and a portion of toluene (275 kg, 2.24 w/w) is added to afford a suspension. The suspension is refluxed at 110 – 120 °C for 23 – 25 h. The mixture is cooled to 22 °C and washed twice with aqueous NH_4Cl (10%, 301.2 kg, 0.72 eq.) and once with aqueous $NaHCO_3$ (5%, 301.2 kg, 0.23 eq., check pH 8 – 9). The solvent is removed at 125 – 135 °C and atmospheric pressure to a target volume of 256 L, the mixture is filtered over celite, the cake is washed with toluene (25 kg). The resulting mixture containing compound 3-A is used directly in the next step without isolation. The yield is determined by correcting for the LOD and GC-FID purity of the sample (208.4 kg, 90.0% corrected, 0.89% Compound 2-A). EI-MS: 294.1 $[M-H]^+$, 190.1 $[M-C_6H_5CH(CH_3)]^+$, 105.1 $[C_6H_5CH(CH_3)]^+$.

Step 2: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)-N-((*S*)-1-phenylethyl)ethan-1-amine hydrochloride (Compound 4-A)

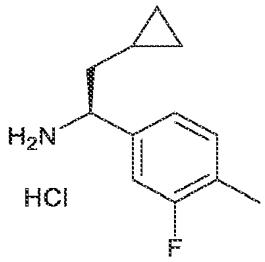


Compound 4-A

Sponge nickel catalyst (144 kg, 0.70 w/w, shipped as a 50% w/w suspension in water) is added to a hydrogenation reactor, equipped with a dip tube capable of removing material from the top of the mass inside, minimizing the amount of water introduced. The supernatant is discarded, ethanol (329.3 kg, 1.58 w/w, anhydrous) is added, the suspension is stirred and then allowed to settle. This process is repeated four more times and the Karl Fisher (KF) of the supernatant is checked (≤ 1% H_2O w/w). Compound 3-A (208.4 kg, 1 eq., as a 62.6% solution in toluene) is added to the mixture in the hydrogenation reactor and ethanol (387.6 kg, 1.86 w/w) is used to rinse the addition flask into the hydrogenation reactor. The hydrogenation reactor is pressurized/depressurized twice with nitrogen (2 bar) and twice with hydrogen (5 bar) then pressurized with hydrogen (9.8 – 10.2 bar) and heated to 33 – 37 °C and stirred for 17 – 19 h. The system is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed with three times with ethanol (493.8 kg, 2.37 w/w). HCl (concentrated, 83.4 kg, 1.07 eq.) is added and the mixture stirred 25 – 35 min at 20

– 24 °C. The mixture is concentrated by distillation at 78 – 80 °C and atmospheric pressure to remove water with a distillate target volume of 1167 L (5.6 L/kg, Compound 3-A) and the KF of the solution is checked (≤ 1.5% H_2O w/w). The mixture is stirred at 48 – 52 °C for 55 - 65 min, then 68 – 72 °C for 55 – 65 min, then cooled to 20 – 24 °C at a rate of 12 °C/h and stirred for 25 – 35 min, then cooled to 0 – 4 °C at a rate of 10 °C/h and stirred for 55 – 65 min. The suspension is filtered, the cake is washed twice with precooled ethanol (329.2 kg, 1.58 w/w, 0 °C), and the collected solid is dried at 40 °C to afford compound 4-A (156.5 kg, 66.4% uncorrected). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm -0.33 - -0.06 (m, 2 H) 0.11 - 0.31 (m, 3 H) 1.57 (d, *J*=6.57 Hz, 3 H) 1.95 (br t, *J*=7.07 Hz, 2 H) 2.26 (d, *J*=1.26 Hz, 3 H) 3.68 (br d, *J*=7.83 Hz, 1 H) 3.92 (br t, *J*=6.44 Hz, 1 H) 6.98 (dd, *J*=7.71, 1.14 Hz, 1 H) 7.28 - 7.36 (m, 2 H) 7.37 - 7.50 (m, 5 H). ESI-MS: 298.2 m/z $[M+H]^+$.

Step 3: Preparation of (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine hydrochloride (Compound 5-A)

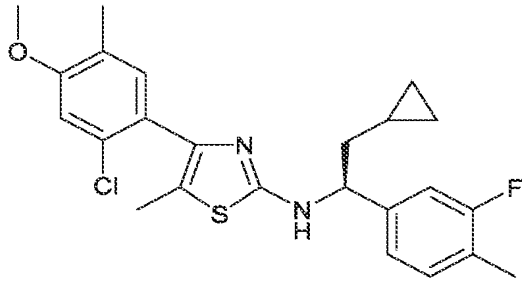


Compound 5-A

Compound 4-A (156.5 kg, 1.00 eq.) and Pd/C (7.8 kg, 10% Pd basis) are added to an inerted hydrogenation reactor. The reactor is then pressurized/depressurized twice with nitrogen (2 bar) and then methanol (494.5 kg, 3.16 w/w) is added. The reactor is depressurized/pressurized three times with nitrogen (2 bar) then three times with hydrogen (5 bar), pressurized with hydrogen (9.8 – 10.2 bar), heated to 58 – 62 °C and stirred for 7 – 9 h. The reaction mixture is cooled to 20 – 24 °C. The reactor is depressurized/pressurized three times with nitrogen (1 bar) and the suspension is filtered and washed three times with methanol (492.9 kg, 3.15 w/w). The solution is concentrated at 63 – 67 °C and atmospheric pressure to a distillate target volume of 1408 L (9.0 L/kg Compound 4-A). *n*-Heptane (1173.8 kg, 7.5 w/w) is added and the mixture is refluxed at 65 – 80 °C and atmospheric pressure in Dean-Stark configuration to remove methanol. The suspension is cooled to 31 – 35 °C and filtered, the cake washed with *n*-heptane (147.1 kg, 0.94 w/w), and the solid dried at 40 °C

(101.0 kg, 93.8% uncorrected, 99.2% *ee*). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm -0.12 - 0.14 (m, 2 H) 0.26 - 0.42 (m, 2 H) 0.44 - 0.55 (m, 1 H) 1.70 - 1.83 (m, 2 H) 2.23 (d, *J*=1.52 Hz, 3 H) 4.24 (t, *J*=7.33 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.29 - 7.36 (m, 1 H) 7.40 (dd, *J*=10.99, 1.39 Hz, 1 H). ESI-MS: 194.2 $[M+H]^+$, 177.0 $[M-NH_2]^+$.

Step 4: Preparation of (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (Compound 7-A)

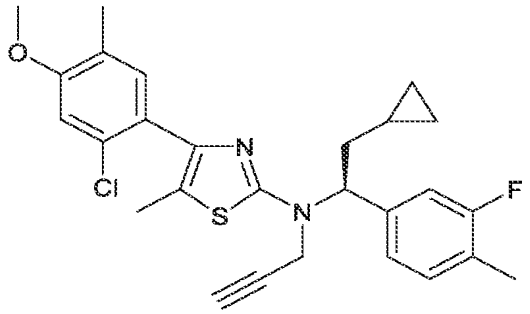


Compound 7-A

A mixture of *n*-heptane (146 kg), water (142 kg), Compound 5-A (57.4 kg), and aqueous sodium hydroxide (30% w/w, 41.0 kg) was stirred together. The layers were partitioned, and the aqueous layer removed. The organic layer was washed with water (170 kg) and the layers partitioned. The organic layer was set aside using n-heptane (40 kg) to rinse and n-heptane (145 kg) and 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (6-A, 66.1 kg) were added to the reactor and heated to 85 °C. The previously set aside organic layer containing the free base of Compound 5-A was added at 84 – 85 °C to the reactor and rinsed with n-heptane (20 kg). The resulting mixture was stirred for 2 h at 83 °C. Subsequently, the solvent was switched to methanol by four put-and-take additions/vacuum distillations of methanol (180 kg) at 55 °C with the target volume being 287 L remaining in the reactor. The suspension was cooled to 5 °C and water (570 kg) was added over 4 h at 5 – 10 °C, with the first 60 kg added very slowly. The suspension was aged 2 h at °C and then isolated by filtration and washed with a mixture of methanol/water (91/115 kg) and then a mixture of methanol/water (134/57 kg). The yellow solid was dried at 25 °C and 1 mbar for 17 h then 40 °C and 1 mbar for 22 h to afford Compound 7-A (97.4 kg, 87.5% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm -0.01 - 0.14 (m, 2 H) 0.29 - 0.42 (m, 2 H) 0.61 - 0.73 (m, 1 H) 1.47 (dt, *J*=13.83, 6.85 Hz, 1 H) 1.76 (dt, *J*=13.89, 7.20 Hz, 1 H) 2.00 (s, 3 H) 2.11 (s, 3 H) 2.19 (d, *J*=1.01 Hz, 3 H) 3.82 (s, 3 H) 4.54 (q, *J*=7.58 Hz, 1 H) 7.00 (s,

1 H) 7.06 (d, *J*=0.76 Hz, 1H) 7.08 - 7.14 (m, 2 H) 7.18 - 7.23 (m, 1 H) 7.89 (d, *J*=8.08 Hz, 1 H). ESI-MS: 445.3 m/z $[M+H]^+$.

Step 5: Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I))



Compound of Formula (I)

A mixture of MTBE (279 kg), tetra-n-butylammonium bromide (10.5 kg), and Compound 7-A (95.4 kg) were heated at 60 °C external temperature for 30 min and then cooled to 0 °C. Aqueous potassium hydroxide (52.4% w/w, 364 kg) and propargyl bromide (39.4 kg as an 80% w/w solution in toluene, 1.19 eq.) were added at 0 – 5 °C and the biphasic mixture aged 14.5 h at 4 – 6 °C with vigorous stirring. Subsequently, water (191 kg) was added and the aqueous layer was discharged. The organic layer was washed twice with water (382 kg) and once with aqueous acetic acid (5.26% w/w, 190 kg) at 20 °C. The mixture is polish filtered, rinsed with ethanol (11 kg) and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol (300 kg) at 25 – 30 °C for the first cycle and then 35 – 40 °C with the target volume of each cycle being 250 L remaining in the reactor. Ethanol (164 kg) was added and the mixture heated at 60 °C external for 0.5 h before it was cooled to 25 °C in 1 h and seeded with authentic compound of Formula (I) (0.340 kg) which may be prepared as described below in Example 15B. The suspension was aged for 5 h, cooled to 0 °C in 2 h, aged 12 h, filtered, and washed twice with ethanol (24 kg each) pre-cooled to 0 °C. The white solid was dried at 40 °C and 1 mbar for 19 h to yield 80.15 kg of the compound of Formula (I), Form I (77.2% yield). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.14 (qt, *J*=8.59, 4.42 Hz, 2 H) 0.29 - 0.48 (m, 2 H) 0.61 - 0.82 (m, 1 H) 1.89 (dt, *J*=14.08, 6.98 Hz, 1 H), 2.07 (br d, *J*=7.83 Hz, 1 H) 2.10 (s, 3 H) 2.14 (s, 3 H) 2.20 (d, *J*=1.01 Hz, 3 H)

3.11 (t, *J*=2.27 Hz, 1 H) 3.83 (s, 3 H) 3.94 - 4.22 (m, 2 H) 5.26 (t, *J*=7.58 Hz, 1 H) 7.05 (s, 1 H) 7.10 - 7.36 (m, 4 H). ESI-MS: 483.2 m/z $[M+H]^+$.

The crystallinity of the crystalline free base Compound of Formula (I), Form I was confirmed by XRPD (Figure 25, Table 44) and further supported by DSC (Figure 26), indicating the crystalline compound having an onset of melt at about 84.4 °C (71.9 J/g). TGA of the crystalline free base exhibited about 0.6% of weight loss due to solvent/H_2O.

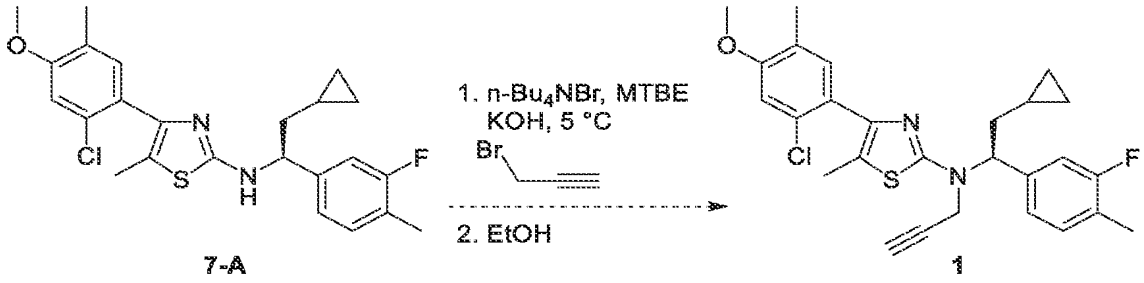
Table 44. XRPD Peak Data for the Compound of Formula (I) Crystalline Free Base Form I

2-Theta (°)	Height (cps)
5.901(15)	1221(101)
10.367(11)	1280(103)
11.762(13)	1377(107)
12.582(11)	1591(115)
13.802(2)	7326(247)
14.1541(16)	20179(410)
15.173(14)	449(61)
15.854(7)	2906(156)
16.746(5)	5113(206)
18.366(7)	1171(99)
19.586(2)	27789(481)
20.100(4)	10759(299)
20.794(4)	5441(213)
21.730(5)	7125(244)
22.239(7)	10370(294)
23.056(11)	3482(170)
23.714(7)	2300(138)
24.115(7)	8402(265)
25.666(4)	26173(467)
26.296(6)	1505(112)
26.752(4)	9919(288)
27.264(7)	1016(92)
27.874(7)	2092(132)
28.623(3)	10560(297)
29.546(6)	5811(220)
30.025(3)	2248(137)
30.737(10)	1333(105)
31.017(19)	1406(108)
31.588(10)	2292(138)
31.809(8)	2212(136)
32.126(13)	593(70)
33.200(16)	839(84)
33.613(13)	2996(158)

2-Theta (°)	Height (cps)
33.914(13)	1156(98)
34.276(16)	1008(92)
34.564(12)	1056(94)
35.397(18)	816(82)
36.073(10)	1928(127)
36.67(3)	562(68)
37.347(9)	1553(114)
37.776(12)	1573(114)
39.070(7)	1890(125)
39.743(15)	1042(93)
40.643(9)	2808(153)
41.106(8)	1107(96)
41.984(11)	2686(150)
42.376(16)	986(91)
42.901(16)	492(64)
43.543(10)	4744(199)
44.419(16)	2810(153)

Example 15B

Preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-(2-propyn-1-yl)-2-thiazolamine (Compound of Formula (I), seed batch)



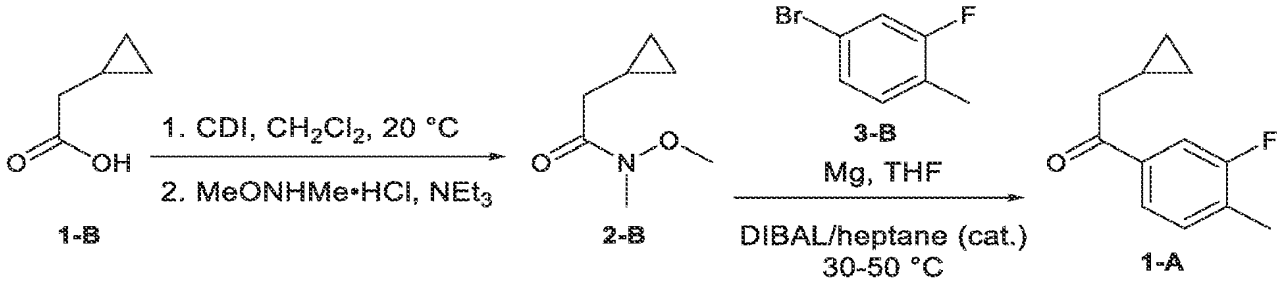
A mixture of MTBE, *tetra*-n-butylammonium bromide, and Compound 7-A cooled to 0 °C is treated with aqueous potassium hydroxide and propargyl bromide maintaining the temperature at 0 – 5 °C. The resulting biphasic mixture is aged 23 h at 4 – 6 °C. Subsequently, water and MTBE are added and the aqueous layer is discharged. The organic layer is washed twice with water and once with aqueous acetic acid at 20 °C. Ethanol is added and then the solvent switched to ethanol by 3 put-and-take additions/vacuum distillations of ethanol at 35 – 40 °C with a target volume of each cycle remaining in the vessel, except for the third cycle where the mixture is concentrated to dryness. Ethanol is added to the vessel and the mixture heated at 60 °C external for 0.5 h before it is cooled to 20

°C in 1 h and aged 18 h affording a suspension. The suspension is cooled to 0 °C, aged 6 h, filtered, and washed twice with ethanol pre-cooled to 0 °C to afford a solid. The solid is dried at 40 °C under vacuum to afford the compound of Formula (I).

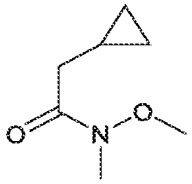
Example 15C

Scheme 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)

Scheme 2



Step 1: Preparation of 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (Compound 2-B)

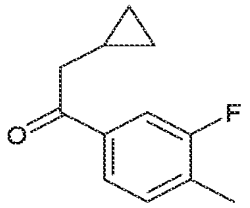


Compound 2-B

A suspension of 1,1'-Carbonyldiimidazole (152.6 kg, 1.01 eq.) in DCM (682 kg, 513 L, 7.3 w/w relative to 2-cyclopropylacetic acid) was treated with a solution of 2-cyclopropylacetic acid (1-B, 93.6 kg, 1 eq.) in DCM (248 kg, 186 L, 2.65 w/w) over at least 1 h, keeping the temperature ≤ 25 °C and compensating for significant effervescence. The resulting mixture is stirred for 15 min at 22 °C and then *N,O*-dimethylhydroxylamine•HCl (93.3 kg, 1.03 eq.) is added in portions, keeping the temperature ≤30 °C. Subsequently, triethylamine (46.4 kg, 0.49 eq.) is added to the stirring mixture at 20 - 25 °C. The resulting mixture is stirred at 22 °C at least 1 h. The mixture is washed once with $KHSO_4$ solution (0.24 M, 357.1 kg, 0.09 eq.), once with $KHSO_4$ solution (0.40 M, 365.4 kg, 0.15 eq.), once with $KHSO_4$ solution (0.80 M, 384.5 kg, 0.30 eq.), and once with $NaHCO_3$ solution (0.60 M, 393.1 kg, 0.24 eq.). Residual DCM is removed by three put-and-takes of THF (166.6 kg, 1.78 w/w) and vacuum distillation (50 – 60 °C, to minimum volume/until distillation stops). THF (333.2 kg. 3.56 w/w) is added and the yield is determined by correcting for the LOD and GC-

FID purity of the sample (131.5 kg, 98.2% corrected). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ: -0.01 – 0.03 (m, 2H) 0.32 – 0.36 (m, 2H) 0.81 – 0.90 (br m, 1H) 2.18 (d, *J*=6.80 Hz, 2H) 2.97 (s, 3 H) 3.53 (s, 3H). ESI-MS: 144.0 $[M+H]^+$.

Step 2: Preparation of 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (Compound 1-A)



Compound 1-A

Mg (turnings, 28.6 kg, 1.37 eq.) are suspended in THF (244.7 kg, 2.0 w/w) and DIBAL-H (1 M in *n*-heptane, 18.9 kg, 0.03 eq.) is added dropwise at 30 °C, The resulting mixture is stirred at 30 °C for at least 10 min and then 4-bromo-2-fluoro-1-methylbenzene (3-B, neat, 21.1 kg, 0.13 eq.) is added over at least 30 min at 30 – 50 °C. Subsequently, the mixture is treated with a solution of 4-bromo-2-fluoro-1-methylbenzene (3-B, 191.6 kg, 1.18 eq.) in THF (414.5 kg, 3.37 w/w) at 30 – 50 °C over 3 h or less. The mixture is stirred at 30 °C for at least 1 h. Subsequently, the mixture is treated with 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (2-B, 123.0 kg, 1 eq., 25.9% w/w solution in THF) over at least 1 h at 15 – 25 °C. The resulting mixture is stirred at 20 – 25 °C for at least 1 h. The stirring mixture is then treated with aqueous HCl (3 M, 10.3% w/w, 668.9 kg, 2.24 eq.) at 10 - 25 °C and the resulting mixture is stirred at least 2 h (check pH 3.0 – 3.5). The layers are separated, and the aqueous layer is combined with heptane (290.3 kg, 2.36 w/w). The layers are separated, and the organic layer is washed once with $NaHCO_3$ solution (0.63 M, 211.6 kg, 0.15 eq.) and once with NaCl solution (2.57 M, 213.0 kg, 0.55 eq.). The residual solvents are removed by vacuum distillation at 58 - 62 °C until distillation stops and then one put-and-take of toluene (275.5 kg, 2.24 w/w) at 107 – 117 °C until distillation stops. Toluene (275.5 kg, 2.24 w/w) is added and the yield is determined by correcting for the LOD and GC-FID purity of the sample (150.7 kg, 91.3% corrected). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.07 - 0.21 (m, 2 H) 0.40 - 0.54 (m, 2 H) 1.02 (ttt, *J*=8.16, 8.16, 6.68, 6.68, 4.86, 4.86 Hz, 1 H) 2.30 (d, *J*=1.77 Hz, 3 H) 2.91 (d, *J*=6.57 Hz, 2 H) 7.44 (t, *J*=7.83 Hz, 1 H) 7.57 - 7.78 (m, 2 H). ESI-MS: 193.1 $[M+H]^+$.

Example 16: Compound of Formula (I) Crystalline Tosylate Salt Form 1

Approximately 20 mg of the Compound of Formula (I) was weighed into a vial. Using a positive displacement pipette, 250 µL of solvent (IPA) was added to the vial along with a stir bar. The vial was placed in an aluminum block on a Reacti-Therm mixer and heated to 60 °C for ~1 hour. A molar equivalent of para-toluenesulfonic acid was added to the vial (20 µL of a 2M solution in water) and allowed to stir. The sample was slow cooled back to room temperature along with mild Nitrogen gas for evaporation. Precipitate was collected, left to dry overnight, and then analyzed by XRPD, DSC, and TGA.

The crystallinity of the crystalline tosylate form 1 was confirmed by XRPD (Figure 27, Table 45) and further supported by DSC (Figure 28), indicating the crystalline compound having an onset of melt at about 156 °C (22.2 J/g). TGA of the crystalline compound is provided in Figure 28, and exhibited about 0.5% of weight loss due to solvent/H_2O.

Table 45. XRPD Peak Data for the Compound of Formula (I) Crystalline Tosylate Form 1

2-Theta (°)	Height (cps)
8.112(9)	957(89)
9.124(2)	12296(320)
9.471(2)	4519(194)
10.525(3)	8507(266)
11.316(3)	10211(292)
13.182(5)	6158(227)
13.494(6)	1598(115)
14.249(9)	2197(135)
15.208(9)	1746(121)
15.711(7)	1437(109)
16.252(5)	5723(218)
16.692(3)	3848(179)
17.540(4)	1578(115)
19.031(6)	6774(238)
19.265(4)	6491(233)
19.499(10)	3152(162)
20.401(3)	8581(267)
20.656(4)	3040(159)
21.142(3)	11498(310)
21.703(6)	4979(204)
21.870(11)	5331(211)
22.277(5)	3701(176)
22.769(3)	10159(291)

2-Theta (°)	Height (cps)
23.297(3)	14954(353)
23.532(4)	3597(173)
23.810(3)	9590(283)
24.73(2)	2325(139)
25.47(4)	1704(119)
26.087(5)	2413(142)
26.71(3)	422(59)
27.210(6)	1648(117)
27.593(5)	2825(153)
28.472(4)	6417(231)
29.51(3)	1423(109)
29.98(3)	849(84)
30.63(6)	1262(103)
30.77(3)	1121(97)
31.577(3)	5563(215)
32.74(4)	874(85)
33.73(4)	1111(96)
34.415(13)	2054(131)
34.799(11)	706(77)
35.139(15)	1320(105)
35.682(16)	1028(93)
38.39(4)	751(79)
39.743(17)	1790(122)
40.219(16)	762(80)
41.23(3)	925(88)
43.16(3)	1540(113)
44.288(12)	1142(98)

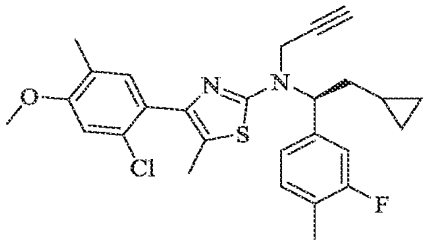
OTHER EMBODIMENTS

It is to be understood that the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

2. The pharmaceutical composition of claim 1, comprising about 1 wt% to about 20 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

3. The pharmaceutical composition of claim 1, comprising about 5 wt% to about 15 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

4. The pharmaceutical composition of claim 1, comprising about 10 wt% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

5. The pharmaceutical composition of any one of claims 1-4, comprising an oily phase vehicle.

6. The pharmaceutical composition of any one of claims 1-5, comprising about 1 wt% to about 50 wt% of the oily phase vehicle.

7. The pharmaceutical composition of any one of claims 1-5, comprising about 20 wt% to about 50 wt% of the oily phase vehicle.

8. The pharmaceutical composition of any one of claims 1-5, comprising about 35 wt% to about 45 wt% of the oily phase vehicle.

9. The pharmaceutical composition of any one of claims 1-5, comprising about 39 wt% of the oily phase vehicle.

10. The pharmaceutical composition of any one of claims 1-9, wherein the oily phase vehicle is selected from medium-chain triglycerides, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

11. The pharmaceutical composition of any one of claims 1-10, wherein the oily phase vehicle is medium-chain triglycerides.

12. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Labrafac TM Lipophile WL1349.

13. The pharmaceutical composition of any one of claims 10-11, wherein the medium-chain triglycerides are Miglyol 812N.

14. The pharmaceutical composition of any one of claims 1-13, comprising an emulsifying agent.

15. The pharmaceutical composition of any one of claims 1-14, comprising about 5 wt% to about 50 wt% of the emulsifying agent.

16. The pharmaceutical composition of any one of claims 1-14, comprising about 10 wt% to about 30 wt% of the emulsifying agent.

17. The pharmaceutical composition of any one of claims 1-14, comprising about 15 wt% to about 25 wt% of the emulsifying agent.

18. The pharmaceutical composition of any one of claims 1-14, comprising about 20 wt% of the emulsifying agent.

19. The pharmaceutical composition of any one of claims 1-18, wherein the emulsifying agent is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

20. The pharmaceutical composition of any one of claims 1-19, wherein the emulsifying agent is propylene glycol dicaprylate/dicaprate.

21. The pharmaceutical composition of any one of claims 19-20, wherein the propylene glycol dicaprylate/dicaprate is Labrafac TM PG.

22. The pharmaceutical composition of any one of claims 1-21, comprising a nonionic surfactant.

23. The pharmaceutical composition of any one of claims 1-22, comprising about 5 wt% to about 50 wt% of the nonionic surfactant.

24. The pharmaceutical composition of any one of claims 1-22, comprising about 10 wt% to about 30 wt% of the nonionic surfactant.

25. The pharmaceutical composition of any one of claims 1-22, comprising about 15 wt% to about 25 wt% of the nonionic surfactant.

26. The pharmaceutical composition of any one of claims 1-22, comprising about 19 wt% of the nonionic surfactant.

27. The pharmaceutical composition of any one of claims 1-26, wherein the nonionic surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, Gelucire, lauroyl polyoxyl-32 glycerides, Poloxamer, PEG-32 stearate, and PEG-32 hydrogenated palm glycerides.

28. The pharmaceutical composition of any one of claims 1-27, wherein the nonionic surfactant is lauroyl polyoxyl-32 glycerides.

29. The pharmaceutical composition of any one of claims 27-28, wherein the lauroyl polyoxyl-32 glycerides are Gelucire® 44/14.

30. The pharmaceutical composition of any one of claims 1-29, comprising a solubilizing agent.

31. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 50 wt% of the solubilizing agent.

32. The pharmaceutical composition of any one of claims 1-30, comprising about 1 wt% to about 20 wt% of the solubilizing agent.

33. The pharmaceutical composition of any one of claims 1-30, comprising about 5 wt% to about 15 wt% of the solubilizing agent.

34. The pharmaceutical composition of any one of claims 1-30, comprising about 11 wt% of the solubilizing agent.

35. The pharmaceutical composition of any one of claims 1-34, wherein the solubilizing agent is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, and Poloxamer.

36. The pharmaceutical composition of any one of claims 1-35, wherein the solubilizing agent is vitamin E polyethylene glycol succinate.

37. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Kolliphor® TPGS.

38. The pharmaceutical composition of any one of claims 35-36, wherein the vitamin E polyethylene glycol succinate is Vitamin E/TPGS 260.

39. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) an oily phase vehicle;

(c) an emulsifying agent;

(d) a nonionic surfactant; and

(e) a solubilizing agent.

40. The pharmaceutical composition of claim 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 35 wt% to about 45 wt% of an oily phase vehicle;

(c) about 15 wt% to about 25 wt% of an emulsifying agent;

(d) about 15 wt% to about 25 wt% of a nonionic surfactant; and

(e) about 5 wt% to about 15 wt% of a solubilizing agent.

41. The pharmaceutical composition of claim 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 39 wt% of an oily phase vehicle;

(c) about 20 wt% of an emulsifying agent;

(d) about 19 wt% of a nonionic surfactant; and

(e) about 11 wt% of a solubilizing agent.

42. The pharmaceutical composition of claim 1, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) a medium-chain triglycerides component;

(c) a propylene glycol dicaprylate/dicaprate component;

(d) a lauroyl polyoxyl-32 glycerides component; and

(e) a vitamin E polyethylene glycol succinate component.

43. The pharmaceutical composition of claim 1, comprising:

(a) about 5 wt% to about 15 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 35 wt% to about 45 wt% of medium-chain triglycerides;

(c) about 15 wt% to about 25 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 15 wt% to about 25 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 5 wt% to about 15 wt% of vitamin E polyethylene glycol succinate.

44. The pharmaceutical composition of claim 1, comprising:

(a) about 10 wt% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine;

(b) about 39 wt% of medium-chain triglycerides;

(c) about 20 wt% of propylene glycol dicaprylate/dicaprate;

(d) about 19 wt% of lauroyl polyoxyl-32 glycerides; and

(e) about 11 wt% of vitamin E polyethylene glycol succinate.

45. The pharmaceutical composition of any one of claims 1-44, wherein the compound of Formula (I), or pharmaceutically acceptable salt thereof, is in crystalline form.

46. The pharmaceutical composition of any one of claims 1-45, comprising the compound of Formula (I) as a free base.

47. The pharmaceutical composition of claim 45, wherein the crystalline form comprises Form I of the compound of Formula (I).

48. The pharmaceutical composition of any one of claims 1-47, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg, based on the weight of the free base.

49. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg, based on the weight of the free base.

50. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg, based on the weight of the free base.

51. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg, based on the weight of the free base.

52. The pharmaceutical composition of claim 48, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 25 mg, based on the weight of the free base.

53. The pharmaceutical composition of any one of claims 1-52, that is in the form of a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

54. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in tablet form.

55. The pharmaceutical composition of any one of claims 48-53, wherein the pharmaceutical composition is in capsule form.

56. The pharmaceutical composition of any one of claims 48-55, wherein the dosage form is coated.

57. A method for preparing the pharmaceutical composition of any one of claims 1-56, comprising:

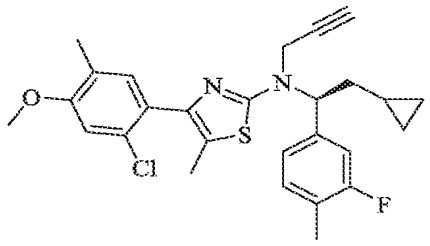
(a) heating a mixture of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent;

(b) mixing the mixture of step (a) until a homogeneous mixture is achieved; and

(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the homogeneous mixture of step (b) until the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is dissolved, forming a composition.

58. The method of claim 57, further comprising:
(d) encapsulating the composition of step (c) in a capsule shell to form a capsule; and
(e) banding the capsule of step (d) in a mixture of banding agent and banding solvent.

59. A pharmaceutical composition in oral solution dosage form comprising:
(a) a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;
(b) one or more of a sweetener, an anti-oxidant, and a flavor; and
(c) a liquid vehicle.

60. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 50 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

61. The pharmaceutical composition of claim 59, comprising about 1 w/v% to about 10 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

62. The pharmaceutical composition of claim 59, comprising about 5 w/v% of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

63. The pharmaceutical composition of any one of claims 59-62, comprising a sweetener.

64. The pharmaceutical composition of any one of claims 59-63, comprising about 0.01 w/v% to about 1.5 w/v% of the sweetener.

65. The pharmaceutical composition of any one of claims 59-63, comprising about 0.1 w/v% to about 0.5 w/v% of the sweetener.

66. The pharmaceutical composition of any one of claims 59-63, comprising about 0.15 w/v% of the sweetener.

67. The pharmaceutical composition of any one of claims 59-66, wherein the sweetener is selected from saccharin, sucrose, sucralose, aspartame, dextrose, fructose, maltitol, mannitol, sorbitol, and avantame.

68. The pharmaceutical composition of any one of claims 59-67, wherein the sweetener is saccharin.

69. The pharmaceutical composition of any one of claims 59-68, comprising an anti-oxidant.

70. The pharmaceutical composition of any one of claims 59-69, comprising about 0.01 w/v% to about 1.5 w/v% of the anti-oxidant.

71. The pharmaceutical composition of any one of claims 59-69, comprising about 0.1 w/v% to about 0.5 w/v% of the anti-oxidant.

72. The pharmaceutical composition of any one of claims 59-69, comprising about 0.17 w/v% of the anti-oxidant.

73. The pharmaceutical composition of any one of claims 59-72, wherein the anti-oxidant is selected from butylated hydroxytoluene, vitamin E TPGS, butylated hydroxyanisole, ascorbic acid, lecithin, tert-butylhydroquinone, and citric acid.

74. The pharmaceutical composition of any one of claims 59-73, wherein the anti-oxidant is butylated hydroxytoluene.

75. The pharmaceutical composition of any one of claims 59-74, comprising a flavor.

76. The pharmaceutical composition of any one of claims 59-75, comprising about 0.01 w/v% to about 0.5 w/v% of the flavor.

77. The pharmaceutical composition of any one of claims 59-75, comprising about 0.05 w/v% to about 0.2 w/v% of the flavor.

78. The pharmaceutical composition of any one of claims 59-75, comprising about 0.10 w/v% of the flavor.

79. The pharmaceutical composition of any one of claims 59-78, wherein the flavor is selected from FONA orange flavor, FONA Juicy Flavor, FONA Grape Flavor, Firmenich SA Lemon Flavor, Firmenich Tetrarome Orange Flavor, IFF Cherry Flavor, and IFF Grape Flavor.

80. The pharmaceutical composition of any one of claims 59-79, wherein the flavor is FONA orange flavor.

81. The pharmaceutical composition of any one of claims 59-80, comprising about 50 w/v% to about 99.9 w/v% of the liquid vehicle.

82. The pharmaceutical composition of any one of claims 59-80, comprising about 92 w/v% to about 97 w/v% of the liquid vehicle.

83. The pharmaceutical composition of any one of claims 59-80, comprising about 94.6 w/v% of the liquid vehicle.

84. The pharmaceutical composition of any one of claims 59-83, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

85. The pharmaceutical composition of any one of claims 59-84, wherein the liquid vehicle is medium-chain triglycerides.

86. The pharmaceutical composition of any one of claims 84-85, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

87. The pharmaceutical composition of any one of claims 59-86, further comprising a surfactant.

88. The pharmaceutical composition of claim 87, comprising about 1 w/v% to about 50 w/v% of the surfactant.

89. The pharmaceutical composition of claim 87, comprising about 10 w/v% to about 30 w/v% of the surfactant.

90. The pharmaceutical composition of claim 87, comprising about 20 w/v% of the surfactant.

91. The pharmaceutical composition of any one of claims 87-90, wherein the surfactant is selected from oleoyl polyoxyl-6 glycerides, linoleoyl polyoxyl-6 glycerides, Polysorbate 80, Polysorbate 20, vitamin E polyethylene glycol succinate, Gelucire, lauroyl polyoxyl-32 glycerides, sodium lauryl sulfate, Poloxamer, corn oil PEG-6 esters, and hydrogenated palm/palm kernel oil PEG-6 esters.

92. The pharmaceutical composition of any one of claims 87-91, wherein the surfactant is oleoyl polyoxyl-6 glycerides.

93. The pharmaceutical composition of any one of claims 91-92, wherein the oleoyl polyoxyl-6 glycerides is LABRAFIL M 1944 CS.

94. The pharmaceutical composition of any one of claims 59-93, comprising about 70 w/v% to about 80 w/v% of the liquid vehicle.

95. The pharmaceutical composition of any one of claims 59-93, comprising about 75 w/v% of the liquid vehicle.

96. The pharmaceutical composition of any one of claims 59-95, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

97. The pharmaceutical composition of any one of claims 59-96, wherein the liquid vehicle is medium-chain triglycerides.

98. The pharmaceutical composition of any one of claims 95-96, wherein the medium-chain triglycerides is Labrafac Lipophile WL1349.

99. The pharmaceutical composition of claim 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) a sweetener;

(c) an anti-oxidant;

(d) a flavor; and

(e) a liquid vehicle.

100. The pharmaceutical composition of claim 99, further comprising a surfactant.

101. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor; and

(e) about 92 w/v% to about 97 w/v% of a liquid vehicle.

102. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor; and

(e) about 94.6 w/v% of a liquid vehicle.

103. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of a sweetener;

(c) about 0.1 w/v% to about 0.2 w/v% of an anti-oxidant;

(d) about 0.05 w/v% to about 0.2 w/v% of a flavor;

(e) about 15 w/v% to about 25 w/v% of a surfactant; and

(f) about 70 w/v% to about 80 w/v% of a liquid vehicle.

104. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of a sweetener;

(c) about 0.17 w/v% of an anti-oxidant;

(d) about 0.1 w/v% of a flavor;

(e) about 20 w/v% of a surfactant; and

(f) about 75 w/v% of a liquid vehicle.

105. The pharmaceutical composition of claim 59, comprising:

(a) 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof;

(b) saccharin;

(c) butylated hydroxytoluene;

(d) FONA orange flavor; and

(e) medium-chain triglycerides.

106. The pharmaceutical composition of claim 105, further comprising oleoyl polyoxyl-6 glycerides.

107. The pharmaceutical composition of claim 106, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor; and

(e) about 92 w/v% to about 97 w/v% of medium-chain triglycerides.

108. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor; and

(e) about 94.6 w/v% of medium-chain triglycerides.

109. The pharmaceutical composition of claim 59, comprising:

(a) about 4 w/v% to about 6 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-

2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.1 w/v% to about 0.2 w/v% of saccharin;

(c) about 0.1 w/v% to about 0.2 w/v% of butylated hydroxytoluene;

(d) about 0.05 w/v% to about 0.2 w/v% of FONA orange flavor;

(e) about 15 w/v% to about 25 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 70 w/v% to about 80 w/v% of medium-chain triglycerides.

110. The pharmaceutical composition of claim 59, comprising:

(a) about 5 w/v% of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) about 0.15 w/v% of saccharin;

(c) about 0.17 w/v% of butylated hydroxytoluene;

(d) about 0.1 w/v% of FONA orange flavor;

(e) about 20 w/v% of oleoyl polyoxyl-6 glycerides; and

(f) about 75 w/v% of medium-chain triglycerides.

111. The pharmaceutical composition of any one of claims 59-110, comprising the compound of Formula (I) as a free base.

112. The pharmaceutical composition of any one of claims 59-111, formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg/mL to about 200 mg/mL, based on the weight of the free base.

113. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg/mL to about 150 mg/mL, based on the weight of the free base.

114. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg/mL, based on the weight of the free base.

115. The pharmaceutical composition of claim 112, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg/mL, based on the weight of the free base.

116. The pharmaceutical composition of any one of claims 1-56, having a viscosity between about 15 to about 40 centipoise at about 45 °C.

117. A method for preparing the pharmaceutical composition of any one of claims 59-116, comprising:

(a) mixing a liquid vehicle with a sweetener;

(b) mixing the mixture of step (a) with an anti-oxidant and a flavor;

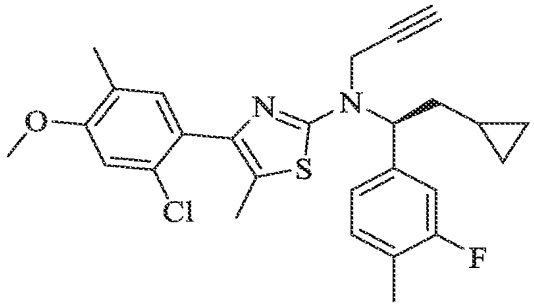
(c) mixing the compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the mixture of step (b); and

(d) mixing the mixture of step (c) with an additional portion of the liquid vehicle.

118. The method of claim 117, wherein step (a) comprises mixing a liquid vehicle with a sweetener and a surfactant.

119. A spray-dried dispersion comprising:

a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and

a polymer selected from a neutral polymer, an enteric polymer, and a pyrrolidone polymer;

wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1 to about 1:9.

120. The spray-dried dispersion of claim 119, wherein the neutral polymer is selected from hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC).

121. The spray-dried dispersion of claim 119, wherein the enteric polymer is selected from hydroxypropyl methyl cellulose acetate succinate (HPMCAS), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), an amino methacrylate copolymer, an ammonioalkyl methacrylate copolymer, and a methacrylic copolymer.

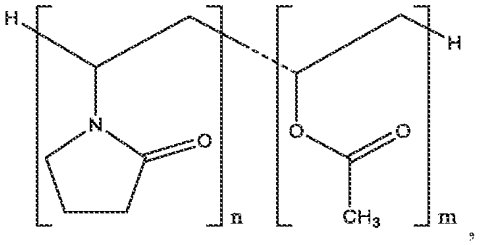
122. The spray-dried dispersion of claim 119, wherein the pyrrolidone polymer is selected from polyvinyl pyrrolidone (PVP) and a polyvinyl pyrrolidone vinyl acetate (PVP/VA).

123. The spray-dried dispersion of claim 122, wherein the pyrrolidone polymer is PVP/VA.

124. The spray-dried dispersion of claim 123, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 40:60 to about 60:40 by weight.

125. The spray-dried dispersion of claim 124, wherein the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight.

126. The spray-dried dispersion of any one of claims 122-125, wherein the copolymer has the structure:

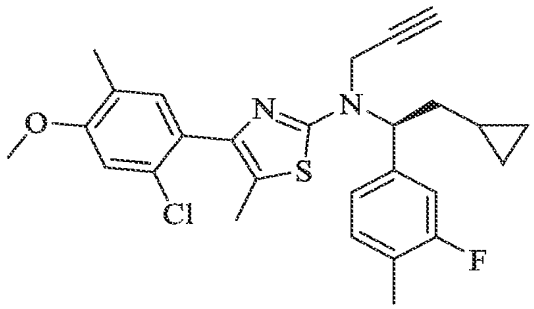


wherein the value of n is about 1 to about 2 times the value of m.

127. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone, wherein the value of n is about 1.16 times the value of m.

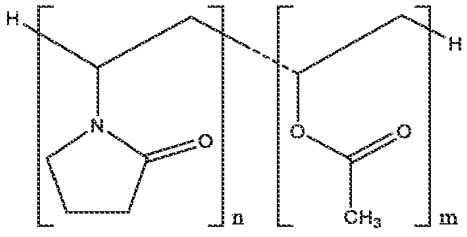
128. The spray-dried dispersion of claim 126, wherein the copolymer is copovidone having an average molecular weight of about 45,000 to about 70,000.

129. A spray-dried dispersion comprising:
a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof; and
a polymer that is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate having the structure:



, wherein the value of n is about 1 to about 2 times the value of m and the copolymer comprises 1-vinyl-2-pyrrolidone and vinyl acetate at a ratio of about 60:40 by weight; and
wherein the weight ratio of the compound of Formula (I) to the copolymer is from about 1:1 to about 1:9.

130. The spray-dried dispersion of any one of claims 119-129, wherein the compound of Formula (I) and the polymer together form homogeneous particles.

131. The spray-dried dispersion of any one of claims 119-130, wherein the particles have a particle size distribution D_{50} of about 5 μm to about 100 μm.

132. The spray-dried dispersion of any one of claims 119-131, wherein the particles have a particle size distribution D_{50} of about 10 μm to about 50 μm.

133. The spray-dried dispersion of any one of claims 119-132, wherein the particles have a particle size distribution D_{50} of about 15 μm to about 30 μm.

134. The spray-dried dispersion of any one of claims 119-133, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:1.5 to about 1:9.

135. The spray-dried dispersion of any one of claims 119-134, wherein the weight ratio of the compound of Formula (I) to the polymer is from about 1:2.5 to about 1:4.

136. The spray-dried dispersion of any one of claims 119-135, wherein the weight ratio of the compound of Formula (I) to the polymer is about 1:3.

137. The spray-dried dispersion of any one of claims 119-136, wherein the particles have a residual solvent content less than about 2 wt %.

138. The spray-dried dispersion of any one of claims 119-137, wherein the particles have a residual solvent content less than about 1 wt %.

139. The spray-dried dispersion of any one of claims 119-138, wherein the particles have a residual solvent content of about 0.5 wt % or less.

140. The spray-dried dispersion of any one of claims 119-139, wherein the compound of Formula (I) in the dispersion is substantially amorphous.

141. A pharmaceutical composition comprising the spray-dried dispersion of any one of claims 119-140 and one or more pharmaceutically acceptable excipients.

142. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 20% to about 90% w/w of the composition.

143. The pharmaceutical composition of claim 142, wherein the spray-dried dispersion is present in an amount of about 40% to about 80% w/w of the composition.

144. The pharmaceutical composition of claim 141, wherein the spray-dried dispersion is present in an amount of about 1% to about 20% w/w of the composition.

145. The pharmaceutical composition of claim 144, wherein the spray-dried dispersion is present in an amount of about 13% w/w of the composition.

146. The pharmaceutical composition of any one of claims 141-145, wherein the pharmaceutical excipients are selected from the group consisting of a filler, a lubricant, and combinations thereof.

147. The pharmaceutical composition of claim 146, wherein the filler is selected from the group consisting of a binder, a diluent, a disintegrant, a glidant, a surfactant, and combinations thereof.

148. The pharmaceutical composition of any one of claims 141-147 formulated in unit dosage form, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 5 mg to about 200 mg.

149. The pharmaceutical composition of claim 148, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 75 mg to about 150 mg.

150. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 50 mg.

151. The pharmaceutical composition of claim 149, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in an amount of about 100 mg.

152. The pharmaceutical composition of any one of claims 141-151, wherein the pharmaceutical excipients are selected from the group consisting of a glidant, a filler, a disintegrant, a lubricant, and a combination thereof.

153. The pharmaceutical composition of any one of claims 141-152, comprising a glidant.

154. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 5 w/w% of the glidant.

155. The pharmaceutical composition of any one of claims 152-153, comprising about 0.1 w/w% to about 1 w/w% of the glidant.

156. The pharmaceutical composition of any one of claims 152-153, comprising about 0.67 w/w% of the glidant.

157. The pharmaceutical composition of any one of claims 152-156, wherein the glidant is selected from calcium silicate, silicon dioxide, and talc.

158. The pharmaceutical composition of any one of claims 152-157, wherein the glidant is calcium silicate.

159. The pharmaceutical composition of any one of claims 141-158, comprising a filler.

160. The pharmaceutical composition of any one of claims 152-159, comprising about 30 w/w% to about 99 w/w% of the filler.

161. The pharmaceutical composition of any one of claims 152-159, comprising about 50 w/w% to about 90 w/w% of the filler.

162. The pharmaceutical composition of any one of claims 152-159, comprising about 75.5 w/w% of the filler.

163. The pharmaceutical composition of any one of claims 152-162, wherein the filler is selected from mannitol, microcrystalline cellulose, lactose, starch, isomalt, silicified microcrystalline cellulose, Dicalcium Phosphate, maltodextrin, and a combination thereof.

164. The pharmaceutical composition of any one of claims 152-163, wherein the filler is a combination of mannitol and microcrystalline cellulose.

165. The pharmaceutical composition of any one of claims 163-164, comprising about 30 w/w% to about 80 w/w% of mannitol.

166. The pharmaceutical composition of any one of claims 163-164, comprising about 50 w/w% to about 60 w/w% of mannitol.

167. The pharmaceutical composition of any one of claims 163-164, comprising about 56 w/w% of mannitol.

168. The pharmaceutical composition of any one of claims 163-167, comprising about 1 w/w% to about 50 w/w% of microcrystalline cellulose.

169. The pharmaceutical composition of any one of claims 163-167, comprising about 10 w/w% to about 30 w/w% of microcrystalline cellulose.

170. The pharmaceutical composition of any one of claims 163-167, comprising about 20 w/w% of microcrystalline cellulose.

171. The pharmaceutical composition of any one of claims 163-167, comprising about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose.

172. The pharmaceutical composition of any one of claims 141-171, comprising a disintegrant.

173. The pharmaceutical composition of any one of claims 152-172, comprising about 1 w/w% to about 30 w/w% of the disintegrant.

174. The pharmaceutical composition of any one of claims 152-172, comprising about 5 w/w% to about 15 w/w% of the disintegrant.

175. The pharmaceutical composition of any one of claims 152-172, comprising about 10 w/w% of the disintegrant.

176. The pharmaceutical composition of any one of claims 152-175, wherein the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, and sodium bicarbonate.

177. The pharmaceutical composition of any one of claims 152-176, wherein the disintegrant is croscarmellose sodium.

178. The pharmaceutical composition of any one of claims 141-177, comprising a lubricant.

179. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 10 w/w% of the lubricant.

180. The pharmaceutical composition of any one of claims 152-178, comprising about 0.1 w/w% to about 1 w/w% of the lubricant.

181. The pharmaceutical composition of any one of claims 152-178, comprising about 0.5 w/w% of the lubricant.

182. The pharmaceutical composition of any one of claims 152-181, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, sodium oleate, glyceryl behenate, and talc.

183. The pharmaceutical composition of any one of claims 152-182, wherein the lubricant is sodium stearyl fumarate.

184. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) the spray-dried dispersion of any one of claims 119-140;

(b) a glidant;

(c) a filler; and

(d) a disintegrant.

185. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of any one of claims 119-140;

(b) about 0.1 w/w% to about 1 w/w% of a glidant;

(c) about 50 w/w% to about 90 w/w% of a filler; and

(d) about 5 w/w% to about 0.2 w/w% of a disintegrant.

186. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) about 13 w/w% of the spray-dried dispersion of any one of claims 119-140;

(b) about 0.67 w/w% of a glidant;

(c) about 75.5 w/w% of a filler; and

(d) about 10 w/w% of a disintegrant.

187. The pharmaceutical composition of any one of claims 141-183, comprising:

(a) the spray-dried dispersion of Example 3;

(b) calcium silicate;

(c) a combination of mannitol and microcrystalline cellulose; and

(d) croscarmellose sodium.

188. The pharmaceutical composition of claim 187, comprising:

(a) about 1 w/w% to about 20 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.1 w/w% to about 1 w/w% of calcium silicate;

(c) about 50 w/w% to about 60 w/w% of mannitol and about 10 w/w% to about 30 w/w% of microcrystalline cellulose; and

(d) about 5 w/w% to about 0.2 w/w% of croscarmellose sodium.

189. The pharmaceutical composition of claim 188, comprising:

(a) about 13 w/w% of the spray-dried dispersion of Example 3;

(b) about 0.67 w/w% of calcium silicate;

(c) about 56 w/w% of mannitol and about 20 w/w% of microcrystalline cellulose; and

(d) about 10 w/w% of croscarmellose sodium.

190. The pharmaceutical composition of any one of claims 141-189 that is formulated as a tablet, capsule, sachet, powder, granules, coated particle, coated tablet, enterocoated tablet, enterocoated capsule, melting strip, or melting film.

191. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in tablet form.

192. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in capsule form.

193. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in sachet form.

194. The pharmaceutical composition of claim 190, wherein the pharmaceutical composition is in granule form.

195. The pharmaceutical composition of any one of claims 190-192, wherein the pharmaceutical composition is coated.

196. A method for preparing the spray-dried dispersion of any one of claims 119-140, comprising:

dissolving the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and the polymer in an organic solvent to form a solution; and

spray-drying the solution to produce the spray-dried dispersion, wherein the spray-drying forms homogeneous particles of the compound of Formula (I) and the polymer.

197. The method of claim 196, comprising removing the organic solvent after formation of the spray-dried dispersion by drying the spray-dried dispersion.

198. The method of claim 197, wherein the spray-dried dispersion is dried with a convection tray dryer.

199. The method of any one of claims 196-198, wherein the organic solvent is acetone.

200. The method of any one of claims 196-199, wherein the spray dryer inlet temperature is about 60°C to about 80°C.

201. The method of claim 200, wherein the spray dryer inlet temperature is about 72°C.

202. The method of any one of claims 196-201, wherein the spray dryer outlet temperature is about 25°C to about 45°C.

203. The method of claim 202, wherein the spray dryer outlet temperature is about 35°C.

204. The method of any one of claims 196-203, wherein the homogeneous particles comprise a bulk density of less than about 0.2 g/mL.

205. The method of claim 204, wherein the homogeneous particles comprise a bulk density of less than about 0.15 g/mL.

206. The method of any one of claims 196-205, wherein the homogeneous particles comprise a tapped density of less than about 0.3 g/mL.

207. The method of claim 206, wherein the homogeneous particles comprise a tapped density of less than about 0.25 g/mL.

208. A method for preparing a pharmaceutical composition, comprising combining the spray-dried dispersion of any one of claims 119-140 with one or more pharmaceutically acceptable excipients.

209. The method of claim 208, comprising:
(a) blending the spray-dried dispersion of any one of claims 119-140, with a glidant;
(b) further blending the blend of step (a) with a filler and a disintegrant;
(c) screening the blend of step (b) to break up aggregates and assist with blend uniformity;
(d) further blending the intragranular blend of step (c);
(e) compaction of the intragranular blend of step (d) via roller compaction to form granules; and
(f) milling of ribbon from roller compaction into granules of step (e).

210. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the spray-dried dispersion of any one of claims 119-140 or the pharmaceutical composition of any one of claims 141-195.

211. The method of claim 210, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject in a fed state.

212. The method of claim 210 or claim 211, wherein the spray-dried dispersion or the pharmaceutical composition is administered to the subject with a nutritional composition.

213. The method of claim 212, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

214. The method of claim 212 or claim 213, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

215. The method of any one of claims 212-214, wherein the nutritional composition is administered within 30 minutes of administration of the spray-dried dispersion or the pharmaceutical composition.

216. The method of any one of claims 211-215, wherein administering the spray-dried dispersion or the pharmaceutical composition exhibits a positive food effect.

217. The method of claim 216, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of the spray-dried dispersion or pharmaceutical composition in the fed and fasting states.

218. The method of any one of claims 211-217, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

219. The method of any one of claims 211-217, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

220. The method of any one of claims 210-219, wherein the subject is a pediatric subject.

221. A method of improving gastrointestinal absorption of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

222. The method of claim 221, wherein the subject is a pediatric subject.

223. A method of improving oral bioavailability of a compound of Formula (I) in a subject, comprising orally administering to the subject the pharmaceutical composition of any one of claims 141-195, wherein the improvement is relative to oral administration of the compound of Formula (I) which has not been prepared as a spray-dried dispersion.

224. The method of claim 223, wherein the subject is a pediatric subject.

225. The spray-dried dispersion of any one of claims 119-140, wherein the spray-dried dispersion is formulated for oral administration and exhibits a positive food effect when administered orally.

226. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the AUC in the fed state to the AUC in the fasted state of about 5 to about 10.

227. The spray-dried dispersion of claim 225, wherein the spray-dried dispersion has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 5 to about 10.

228. A crystalline salt, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, p-toluenesulfonic acid salt.

229. The salt of claim 228, having Form 1 of the Compound of Formula (I).

230. The salt of claim 228 or claim 229, having an X-ray powder diffraction pattern as substantially shown in Figure 27.

231. The salt of any one of claims 228-230, having a DSC thermogram substantially as depicted in Figure 28.

232. The salt of any one of claims 228-231, having a thermogravimetric analysis (TGA) thermogram substantially as depicted in Figure 28.

233. The salt of any one of claims 228-232, having at least one X-ray powder diffraction (XRPD) peak, in terms of 2-theta (± 0.2 degrees), selected 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

234. The salt of any one of claims 228-232, having at least two X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

235. The salt of any one of claims 228-232, having at least three X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

236. The salt of any one of claims 228-232, having at least four X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), selected from 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

237. The salt of any one of claims 228-232, having characteristic X-ray powder diffraction (XRPD) peaks, in terms of 2-theta (± 0.2 degrees), at 9.1, 11.3, 13.2, 16.3 and 21.1 degrees.

238. The salt of any one of claims 228-237, having an endothermic peak having an onset of melt at about 156 °C (22.2 J/g) in a differential scanning calorimetry (DSC) thermogram.

239. A method of treating congenital adrenal hyperplasia in a subject in need thereof comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

240. The method of claim 239, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

241. The method of claim 240, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

242. The method of any one of claims 239-241, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

243. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

244. The method of any one of claims 239-242, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

245. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

246. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

247. The method of any one of claims 239-244, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

248. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 25%.

249. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 30%.

250. The method of any one of claims 239-247, wherein the level of androstenedione is reduced by at least 50%.

251. The method of any one of claims 239-250, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

252. The method of any one of claims 239-251, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

253. The method of any one of claims 239-252, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

254. A method for reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia,

comprising administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in an amount sufficient to reduce the level of androstenedione in the subject.

255. The method of claim 254, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

256. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 25%.

257. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 30%.

258. The method of claim 254 or 255, wherein the androstenedione is reduced by at least 50%.

259. A method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

260. The method of claim 259, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

261. A method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia for controlling congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

262. The method of claim 261, wherein the corticosteroid is a glucocorticoid.

263. A method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia comprising administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof,
wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism, hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

264. The method of any one of claims 259-263, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

265. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

266. The method of any one of claims 259-264, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an

amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

267. The method of any one of claims 259-266, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

268. The method of any one of claims 259-267, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

269. The method of any one of claims 259-268, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

270. A method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii)analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii)administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

271. The method of claim 270, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

272. The method of claim 271, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

273. The method of claim 271 or 272, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

274. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

275. The method of any one of claims 271-273, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

276. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

277. The method of any one of claims 271-275, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

278. The method of any one of claims 270-277, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

279. The method of any one of claims 270-278, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

280. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

281. The method of any one of claims 270-279, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

282. The method of any one of claims 270-281, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

283. A method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, where in the subject is in a fed state.

284. The method of claim 283, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

285. The method of claim 284, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

286. The method of claim 284 or 285, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

287. The method of any one of claims 284-286, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

288. A pharmaceutical composition of any one of claims 1-56, 59-116 or 141-195 for use in a method of treating congenital adrenal hyperplasia (CAH) in a subject.

289. The pharmaceutical composition for use according to claim 288, wherein the subject is in a fed state.

290. The pharmaceutical composition for use according to claim 288 or claim 289, wherein the subject is administered the pharmaceutical composition with a nutritional composition.

291. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising about 1000 to about 2000 calories per liter with a fat content greater than about 30%.

292. The pharmaceutical composition for use according to claim 290, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

293. The pharmaceutical composition for use according to any one of claims 290-292, wherein the nutritional composition is administered in an amount of about 6 to about 12 fluid ounces.

294. The pharmaceutical composition for use according to any one of claims 290-293, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

295. The pharmaceutical composition for use according to any one of claims 290-294, wherein the nutritional composition is administered within 30 minutes of administration of the pharmaceutical composition.

296. The pharmaceutical composition for use according to any one of claims 289-295, wherein administering the pharmaceutical composition exhibits a positive food effect.

297. The pharmaceutical composition for use according to claim 296, wherein the positive food effect is measured in terms of C_{max}, AUC, or a combination thereof of a compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

298. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

299. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

300. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

301. The pharmaceutical composition for use according to any one of claims 289-297, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

302. The pharmaceutical composition for use according to any one of claims 288-301, wherein the subject is a pediatric subject.

303. The pharmaceutical composition for use according to any one of claims 289-295, wherein the pharmaceutical composition exhibits a positive food effect when administered orally.

304. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1 to about 4 or about 5 to about 10.

305. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1 to about 4 or about 5 to about 10.

306. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the AUC in the fed state to the AUC in the fasted state of about 1.5 to about 3.

307. The pharmaceutical composition for use according to claim 303, wherein the compound of Formula (I) has a ratio of the C_{max} in the fed state to the C_{max} in the fasted state of about 1.5 to about 3.

308. The pharmaceutical composition for use according to any one of claims 288-307, wherein the pharmaceutical composition is administered to the subject with a meal.

309. The pharmaceutical composition for use according to claim 308, wherein the meal is a high fat meal.

310. The pharmaceutical composition for use according to claim 308, wherein the meal is a low fat meal.

311. The pharmaceutical composition for use according to any one of claims 308-310, wherein the pharmaceutical composition is administered within about 5 minutes after the start of the meal.

312. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is an evening meal.

313. The pharmaceutical composition for use according to any one of claims 308-311, wherein the meal is a morning meal.

314. The pharmaceutical composition for use according to any one of claims 308-313, wherein administering the pharmaceutical composition exhibits a positive food effect.

315. The pharmaceutical composition for use according to claim 314, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof of the compound of Formula (I) when comparing oral administration of the pharmaceutical composition in the fed and fasting states.

316. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

317. The pharmaceutical composition for use according to any one of claims 308-316, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1 to about 4 or about 5 to about 10.

318. The pharmaceutical composition for use according to any one of claims 308-315, wherein the ratio of the AUC of the compound of Formula (I) in the fed state to the AUC of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

319. The pharmaceutical composition for use according to any one of claims 308-315 or 318, wherein the ratio of the C_{max} of the compound of Formula (I) in the fed state to the C_{max} of the compound of Formula (I) in the fasted state is about 1.5 to about 3.

320. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

321. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

322. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

323. The pharmaceutical composition for use according to any one of claims 288-319, wherein the pharmaceutical composition comprises about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

324. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

325. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

326. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

327. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

328. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 150 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

329. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering a daily dose of the pharmaceutical composition comprising about 200 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

330. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 25 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

331. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 50 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

332. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a dose of about 75 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

333. The pharmaceutical composition for use according to any one of claims 288-319, wherein the method comprises administering the pharmaceutical composition twice daily in a

dose of about 100 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, based on the weight of the free base.

334. The pharmaceutical composition for use according to any one of claims 288-333, wherein the subject is concurrently receiving a dose of a glucocorticoid.

335. The pharmaceutical composition for use according to claim 334, wherein the glucocorticoid is selected from cortisol (hydrocortisone), cortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, fludrocortisone acetate, and deoxycorticosterone acetate.

336. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisol (hydrocortisone).

337. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is cortisone.

338. The pharmaceutical composition for use according to claim 334 or 335, wherein the glucocorticoid is prednisone.

339. The pharmaceutical composition for use according to any one of claims 334-338, wherein the glucocorticoid dose is measured in hydrocortisone equivalents.

340. The pharmaceutical composition for use according to any one of claims 334-339, wherein the glucocorticoid dose is measured as a multiple of the upper limit of normal of physiologic dosing in hydrocortisone equivalents.

341. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose as measured after a time period of administration of the pharmaceutical composition.

342. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 12 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

343. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose of about 4 to about 9 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

344. The pharmaceutical composition for use according to any one of claims 334-340, wherein the glucocorticoid dose is a physiologic dose that is less than about 8 mg/m^2/day as measured after a time period of administration of the pharmaceutical composition.

345. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 10% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition

346. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

347. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

348. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid

dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

349. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

350. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 60% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

351. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 70% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

352. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by less than about 20% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

353. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by about 20% to about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

354. The pharmaceutical composition for use according to any one of claims 334-344, wherein the glucocorticoid dose of the subject is reduced by greater than about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the glucocorticoid dose is relative to the glucocorticoid dose prior to administration of the pharmaceutical composition.

355. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

356. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone is relative to the level of 17-hydroxyprogesterone prior to administration of the pharmaceutical composition.

357. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

358. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits after a time period of administration of the pharmaceutical composition.

359. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

360. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 40% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

361. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of adrenocorticotropic hormone is relative to the level of adrenocorticotropic hormone prior to administration of the pharmaceutical composition.

362. The pharmaceutical composition for use according to any one of claims 288-358, wherein the level of adrenocorticotropic hormone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

363. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of adrenocorticotropic hormone is within normal limits after a time period of administration of the pharmaceutical composition.

364. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

365. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

366. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of androstenedione is relative to the level of androstenedione prior to administration of the pharmaceutical composition.

367. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

368. The pharmaceutical composition for use according to any one of claims 288-363, wherein the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

369. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 25% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

370. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 30% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

371. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of testosterone is relative to the level of testosterone prior to administration of the pharmaceutical composition.

372. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

373. The pharmaceutical composition for use according to any one of claims 288-368, wherein the level of testosterone is within normal limits after a time period of administration of the pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

374. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is reduced by at least about 50% and the level of androstenedione is reduced by at least about 50% after a time period of administration of the pharmaceutical composition, wherein the reduction of the level of 17-hydroxyprogesterone and the level of androstenedione is relative to the level of 17-hydroxyprogesterone and the level of androstenedione prior to administration of the pharmaceutical composition.

375. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is less than about 1.5 times the upper limit of normal and the level of androstenedione is less than about 1.5 times the upper limit of normal after a time period of administration of the pharmaceutical composition.

376. The pharmaceutical composition for use according to any one of claims 288-354, wherein the level of 17-hydroxyprogesterone is within normal limits and the level of androstenedione is within normal limits after a time period of administration of the pharmaceutical composition.

377. The pharmaceutical composition for use according to any one of claims 334-376, wherein the subject exhibits a decrease in glucocorticoid burden after a time period of administration of the pharmaceutical composition, wherein the decrease in glucocorticoid burden is relative to the glucocorticoid burden prior to administration of the pharmaceutical composition.

378. The pharmaceutical composition for use according to claim 377, wherein one or more symptoms of glucocorticoid burden selected from quality of life, fatigue, sleep, insulin resistance, glucose tolerance, glucose control, dyslipidemia, hyperlipidemia, bone mineral density, bone turnover, fat mass, weight, central obesity, blood pressure, hirsutism severity, menstrual cyclicity, control of testicular adrenal rest tumor and fertility, is improved after a time period of administration of the pharmaceutical composition, wherein the improvement in the one or more symptoms is relative to the status of the one or more symptoms prior to administration of the pharmaceutical composition.

379. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 4 weeks.

380. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about 24 weeks.

381. The pharmaceutical composition for use according to any one of claims 341-378, wherein the time period of administration is at least about one year.

382. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is a pediatric subject.

383. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is less than or equal to six years old.

384. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than six years old and less than eleven years old.

385. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than ten years old and less than fifteen years old.

386. The pharmaceutical composition for use according to claim 382, wherein the pediatric subject is greater than fourteen years old and less than nineteen years old.

387. The pharmaceutical composition for use according to any one of claims 288-381, wherein the subject is an adult subject.

388. The pharmaceutical composition for use according to any one of claims 387, wherein the adult subject is over eighteen years old.

389. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is female.

390. The pharmaceutical composition for use according to any one of claims 288-388, wherein the subject is male.

391. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a hydrochloric acid salt or p-toluenesulfonic acid salt.

392. The pharmaceutical composition for use according to any one of claims 288-390, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered as a p-toluenesulfonic acid salt of any one of claims 228-238.

393. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject, wherein the compound, or a pharmaceutically acceptable salt thereof, is administered in an amount sufficient to reduce the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in the subject.

394. The compound of claim 393, wherein the reduction in level of any of biomarkers is determined by comparing the level of the biomarker as measured during the circadian release on a day prior to administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof and the level of the biomarker as measured during

the circadian release on the day after administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

395. The compound of claim 394, wherein the circadian release occurs between the hours of 2 a.m. and 10 a.m.

396. The compound of any one of claims 393-395, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered three to eight hours prior to the circadian release of the biomarker.

397. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 25%.

398. The compound of any one of claims 393-396, wherein the level of 17-hydroxyprogesterone is reduced by at least 50%.

399. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 25%.

400. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 40%.

401. The compound of any one of claims 393-398, wherein the level of adrenocorticotropic hormone is reduced by at least 50%.

402. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 25%.

403. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 30%.

404. The compound of any one of claims 393-401, wherein the level of androstenedione is reduced by at least 50%.

405. The compound of any one of claims 393-401, wherein the level of 17-hydroxyprogesterone is reduced by at least 50% and the level of androstenedione is reduced by at least 50%.

406. The compound of any one of claims 393-405, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

407. The compound of any one of claims 393-406, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

408. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more symptoms selected from hirsutism, precocious puberty, fertility problems, acne, and growth impairment in a subject having classic congenital adrenal hyperplasia, wherein the compound is administered in an amount sufficient to reduce the level of androstenedione in the subject.

409. The compound of claim 408, wherein the growth impairment is selected from one or more of accelerated height velocity, accelerated weight velocity, or accelerated bone age.

410. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 25%.

411. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 30%.

412. The compound of claim 408 or 409, wherein the level of androstenedione is reduced by at least 50%.

413. A compound, which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the level of one or more biomarkers of congenital adrenal hyperplasia in a subject having congenital adrenal hyperplasia.

414. The compound of claim 413, wherein the one or more biomarkers of congenital adrenal hyperplasia are selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

415. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the dosage of corticosteroid administered to a subject having congenital adrenal hyperplasia.

416. The compound of claim 415, wherein the corticosteroid is a glucocorticoid.

417. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of one or more side effects of glucocorticoid treatment in a subject having congenital adrenal hyperplasia, wherein the side effect is selected from osteoporosis, avascular necrosis of bone, myopathy, hyperglycemia, diabetes mellitus, dyslipidemia, weight gain, Cushing syndrome, Cushingoid features, growth suppression, adrenal suppression, gastritis, peptic ulcer, gastrointestinal bleeding, visceral perforation, hepatic steatosis, pancreatitis, hypertension, coronary heart disease, ischemic heart disease, heart failure, dermatoprosis, skin atrophy, ecchymosis, purpura, erosions, striae, delayed wound healing, easy bruising, acne, hirsutism,

hair loss, mood changes, depression, euphoria, mood lability, irritability, akathisia, anxiety, cognitive impairment, psychosis, dementia, delirium, cataract, glaucoma, ptosis, mydriasis, opportunistic ocular infections, central serous chorioretinopathy, suppression of cell-mediated immunity, predisposition to infections, and reactivation of latent infections.

418. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration.

419. The compound of any one of claims 413-418, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

420. The compound of any one of claims 413-417, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof is administered at an amount sufficient to (a) reduce the level of 17-hydroxyprogesterone (17-OHP) by at least 50% as compared to the level prior to administration; and (b) reduce the level of androstenedione by at least 30% as compared to the level prior to administration.

421. The compound of any one of claims 413-420, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

422. The compound of any one of claims 413-421, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

423. The compound of any one of claims 413-422, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

424. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, for use in a method of treating congenital adrenal hyperplasia in a subject comprising

(i)measuring the level of one or more biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione in a biological sample obtained from the subject;

(ii) analyzing the level of the one or more biomarkers to determine if the level of the one or more biomarkers is elevated compared to a healthy subject not having congenital adrenal hyperplasia; and

(iii) administering to the subject 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject is determined to have elevated levels of the one or more biomarkers.

425. The compound of claim 424, further comprising (iv) measuring the level of the one or more biomarkers after administering 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in a biological sample obtained from the subject to determine whether the subject has reduced levels of the one or more biomarkers as compared with the measurement of step (i).

426. The compound of claim 425, further comprising (v) continuing the administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-

methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof if the subject has reduced levels of the one or more biomarkers.

427. The compound of claim 425 or 426, wherein steps (i) and (iv) are performed on biological samples taken from the subject in a similar manner and within a same time of day window.

428. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 2 a.m. to 10 a.m.

429. The compound of any one of claims 425-427, wherein steps (i) and (iv) are performed on biological samples taken from the subject within the time of day window from 6 a.m. to 10 a.m.

430. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of at least two biomarkers selected from (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

431. The compound of any one of claims 425-429, wherein steps (i) and (iv) comprise measuring the levels of (a) 17-hydroxyprogesterone (17-OHP); (b) adrenocorticotropic hormone (ACTH); and (c) androstenedione.

432. The compound of any one of claims 424-431, wherein step (i) comprises measuring the level of 17-hydroxyprogesterone (17-OHP), wherein the level of 17-hydroxyprogesterone (17-OHP) is elevated when it is greater than or equal to 1,000 ng/dL.

433. The compound of any one of claims 424-432, wherein step (i) comprises measuring the level of androstenedione, wherein the level of androstenedione is elevated when it is greater than 200 ng/dL.

434. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-

2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to from about 25 mg to about 150 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

435. The compound of any one of claims 424-433, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered once daily at an amount equivalent to about 50 mg or about 100 mg of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine free base.

436. The compound of any one of claims 424-435, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine is administered in the free base form.

437. A compound which is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof for use in a method of treating congenital adrenal hyperplasia (CAH), in a subject, wherein the subject is in a fed state.

438. The compound of claim 437, wherein the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, is administered to the subject with a nutritional composition.

439. The compound of claim 438, wherein the nutritional composition is a liquid dietary supplement comprising 1500 calories per liter with a caloric distribution of 14.7% protein, 32% fat and 53.3% carbohydrate.

440. The compound of claim 438 or 439, wherein the nutritional composition is administered in an amount of about 8 fluid ounces.

441. The compound of any one of claims 438-440, wherein the nutritional composition is administered within 30 minutes of administration of the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof.

442. The compound of any one of claims 437-441, wherein administering the 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, exhibits a positive food effect.

443. The compound of claim 442, wherein the positive food effect is measured in terms of C_{max}, AUC, or combinations thereof when comparing oral administration of 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine, or a pharmaceutically acceptable salt thereof, in the fed and fasting states.

444. The compound of any one of claims 437-443, wherein the ratio of the AUC in the fed state to the AUC in the fasted state is about 5 to about 10.

445. The compound of any one of claims 437-443, wherein the ratio of the C_{max} in the fed state to the C_{max} in the fasted state is about 5 to about 10.

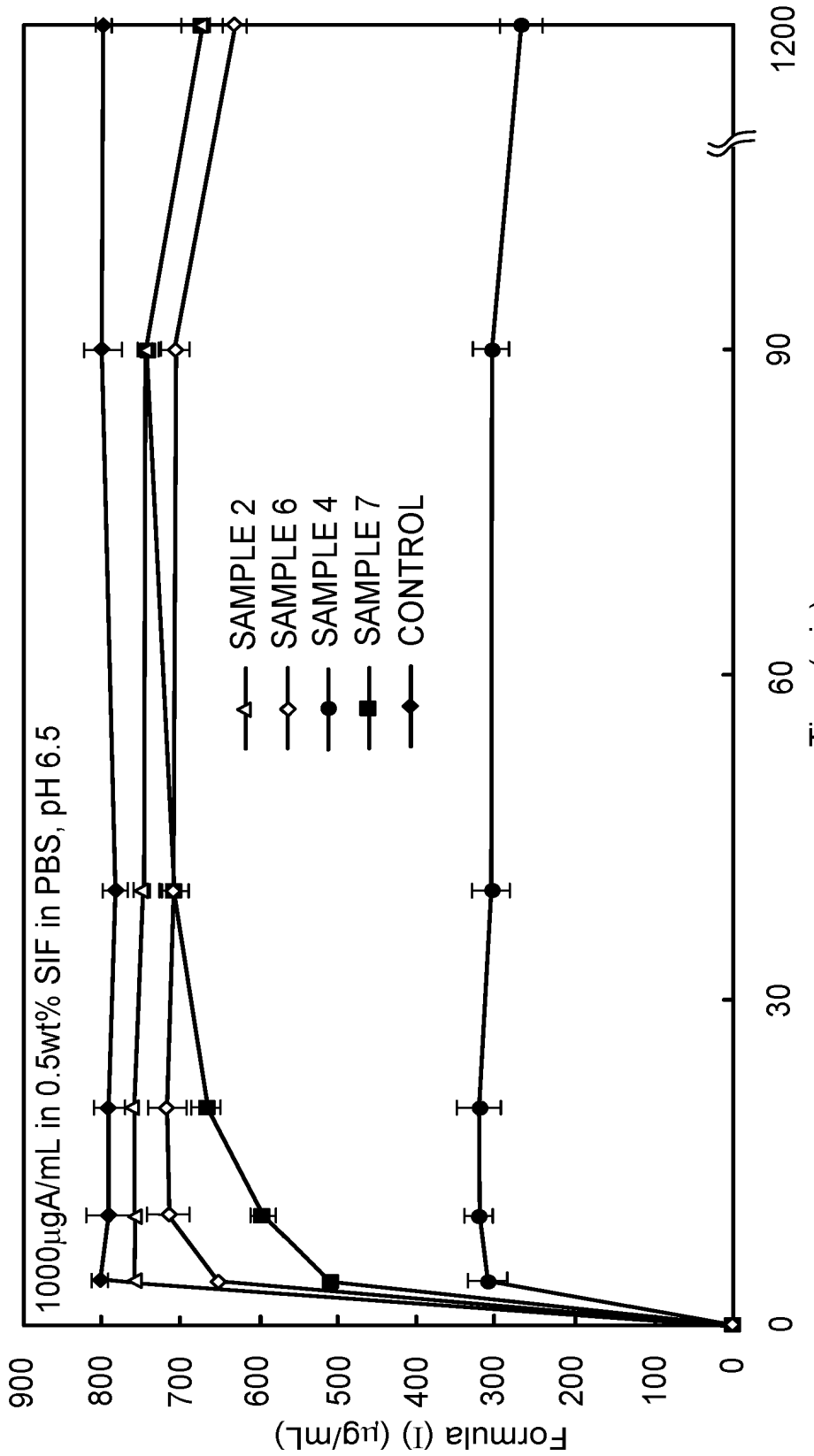

1000μgA/mL in 0.5wt% SIF in PBS, pH 6.5
SAMPLE 2
SAMPLE 6
SAMPLE 4
SAMPLE 7
CONTROL
Formula (I) (μg/mL)
Time (min)
0
100
200
300
400
500
600
700
800
900
0
30
60
90
1200

FIG. 1

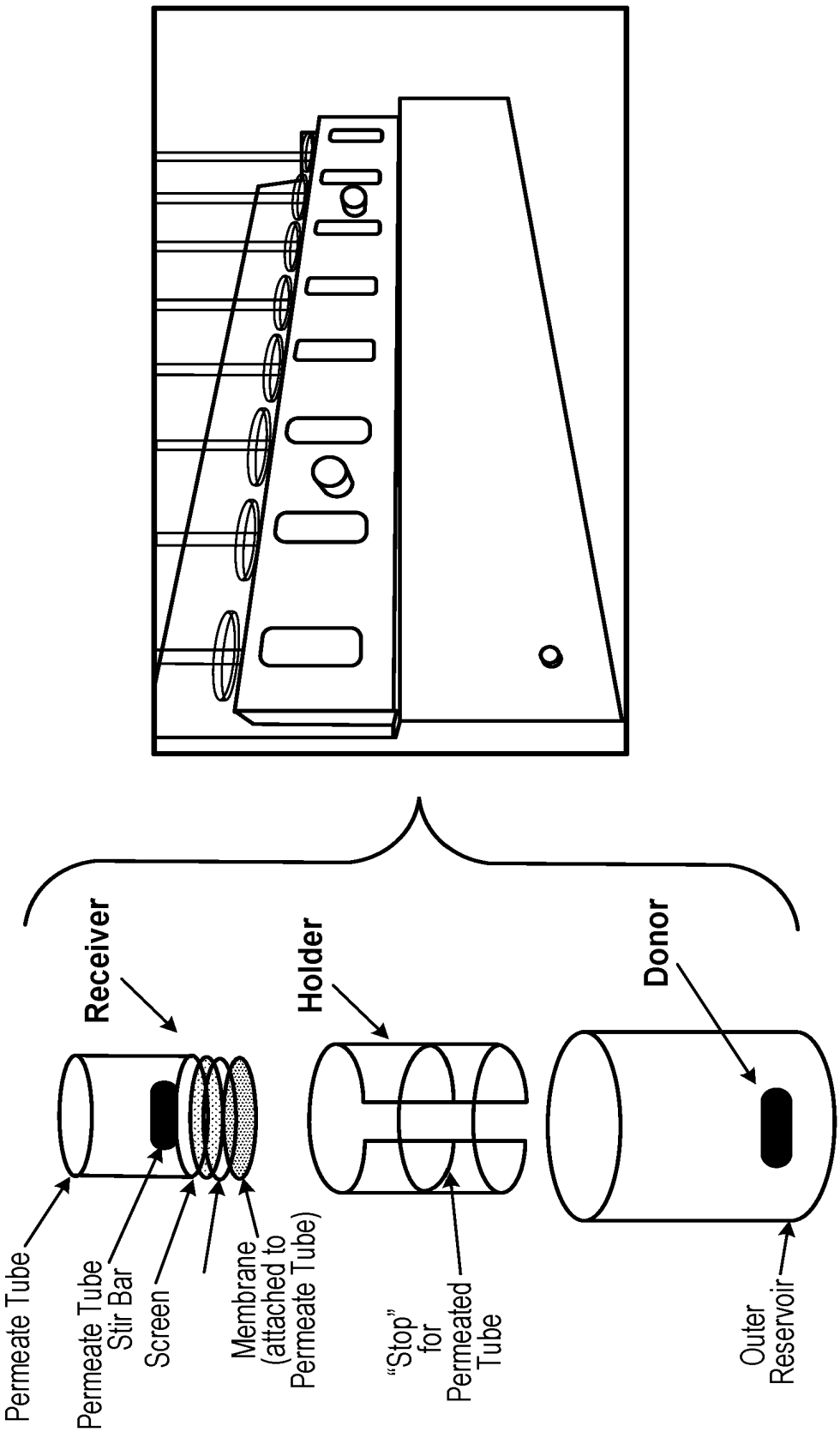

Receiver
Holder
Donor
Permeate Tube
Permeate Tube Stir Bar
Screen
Membrane (attached to Permeate Tube)
"Stop" for Permeated Tube
Outer Reservoir

FIG. 2

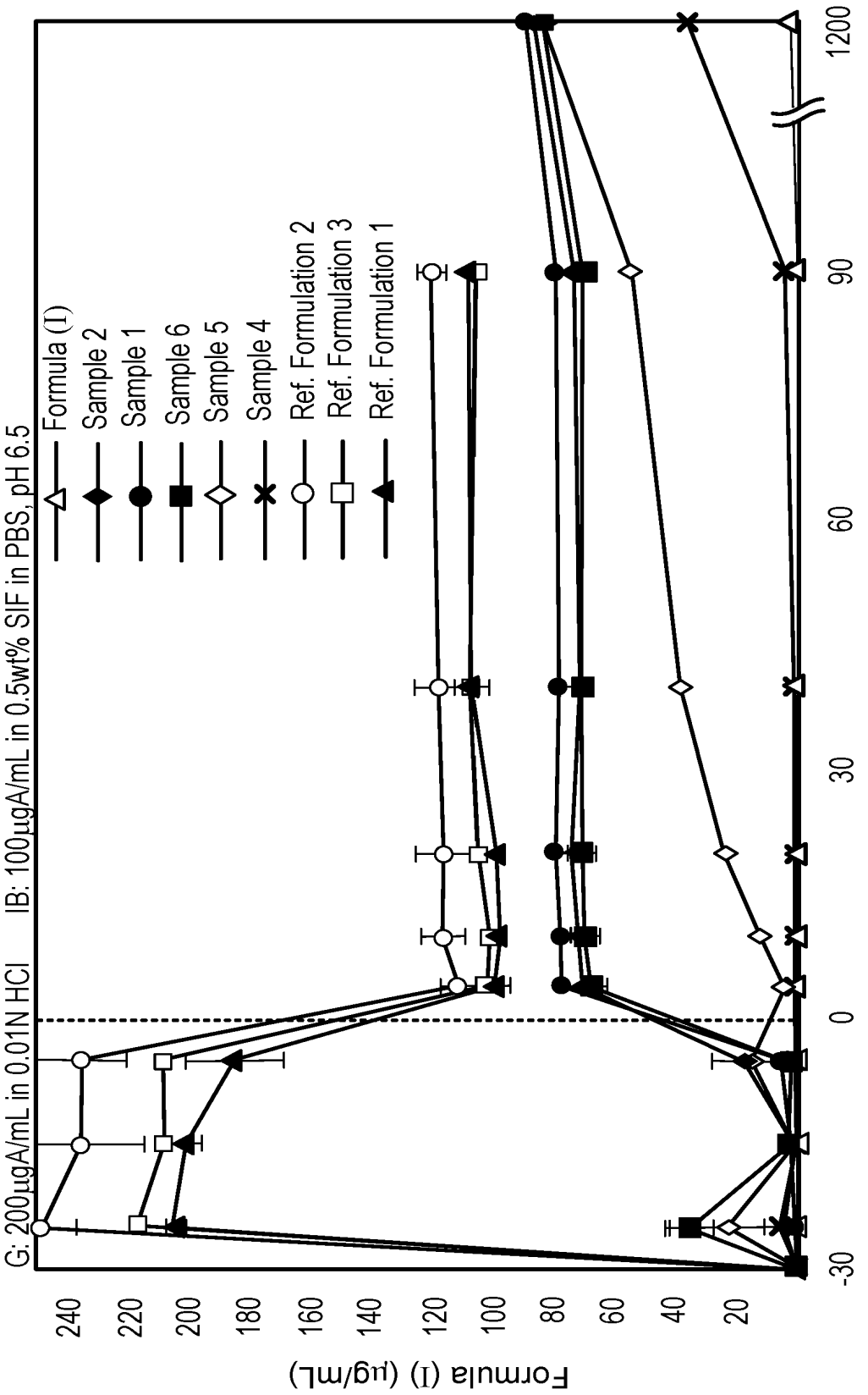

G: 200μgA/mL in 0.01N HCl IB: 100μgA/mL in 0.5wt% SIF in PBS, pH 6.5
Formula (I)
Sample 2
Sample 1
Sample 6
Sample 5
Sample 4
Ref. Formulation 2
Ref. Formulation 3
Ref. Formulation 1
Formula (I) (μg/mL)
240
220
200
180
160
140
120
100
80
60
40
20
-30
0
30
60
90
1200
Time (min)

FIG. 3

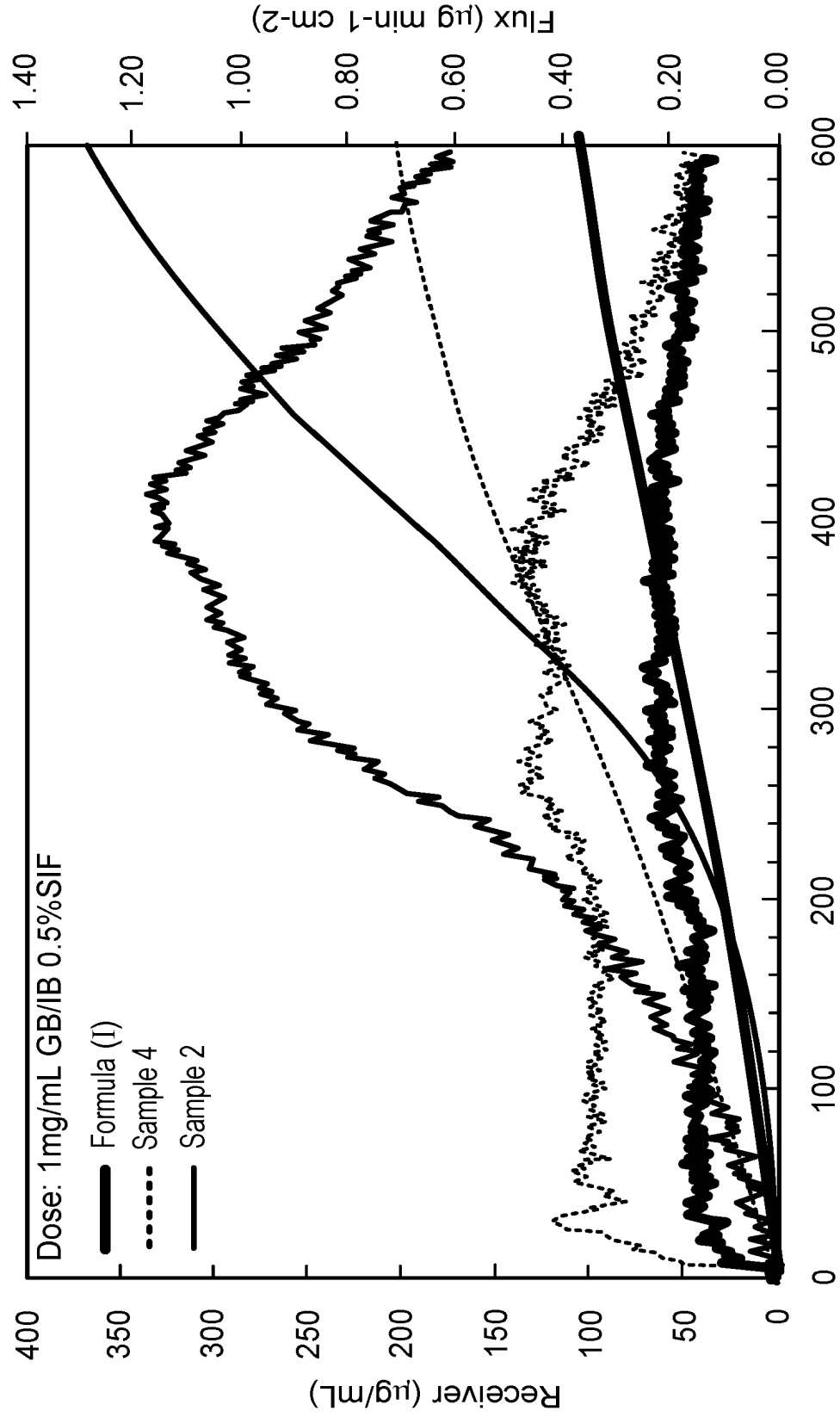

Dose: 1mg/mL GB/IB 0.5%SIF
Formula (I)
Sample 4
Sample 2
Receiver (µg/mL)
Flux (µg min-1 cm-2)
Time (min)
0
50
100
150
200
250
300
350
400
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
0
100
200
300
400
500
600

FIG. 4

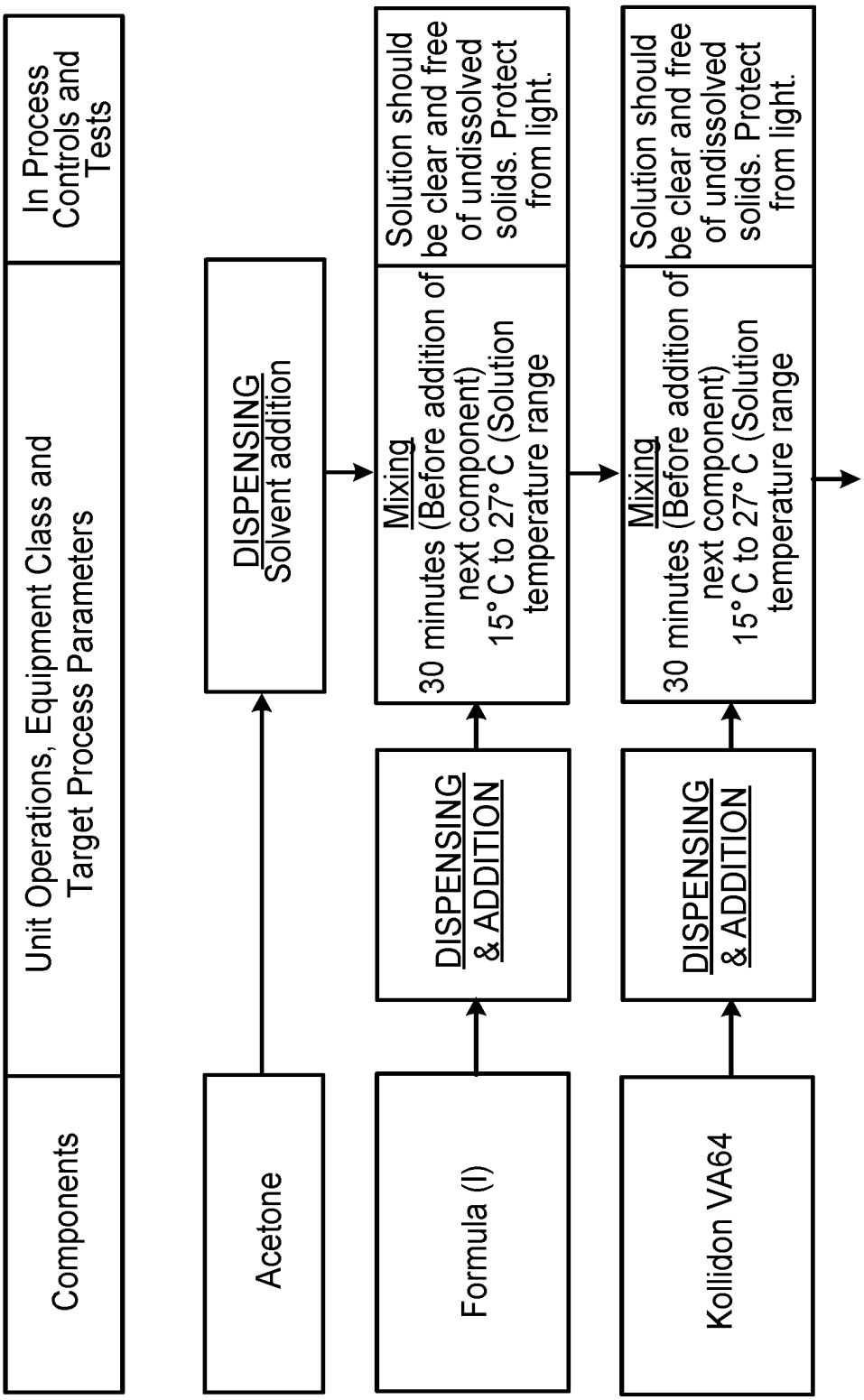

Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Acetone
DISPENSING
Solvent addition
Formula (I)
DISPENSING
& ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.
Kollidon VA64
DISPENSING
& ADDITION
Mixing
30 minutes (Before addition of next component)
15° C to 27° C (Solution temperature range
Solution should be clear and free of undissolved solids. Protect from light.

FIG. 5

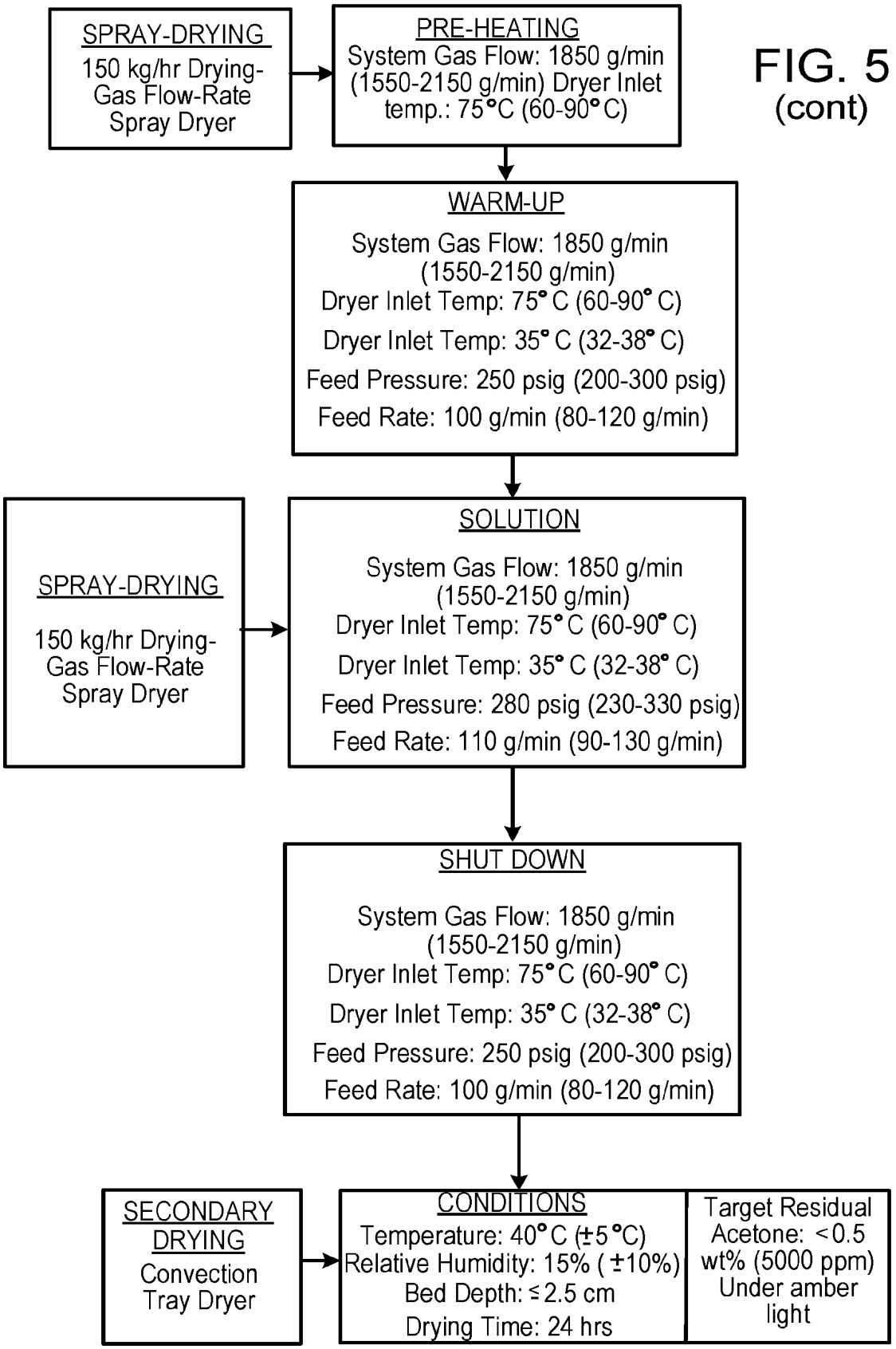

SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
PRE-HEATING
System Gas Flow: 1850 g/min (1550-2150 g/min) Dryer Inlet temp.: 75°C (60-90° C)
WARM-UP
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SPRAY-DRYING
150 kg/hr Drying-Gas Flow-Rate Spray Dryer
SOLUTION
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 280 psig (230-330 psig)
Feed Rate: 110 g/min (90-130 g/min)
SHUT DOWN
System Gas Flow: 1850 g/min (1550-2150 g/min)
Dryer Inlet Temp: 75° C (60-90° C)
Dryer Inlet Temp: 35° C (32-38° C)
Feed Pressure: 250 psig (200-300 psig)
Feed Rate: 100 g/min (80-120 g/min)
SECONDARY DRYING
Convection Tray Dryer
CONDITIONS
Temperature: 40° C (±5 °C)
Relative Humidity: 15% (±10%)
Bed Depth: ≤ 2.5 cm
Drying Time: 24 hrs
Target Residual Acetone: <0.5 wt% (5000 ppm) Under amber light

FIG. 5
(cont)

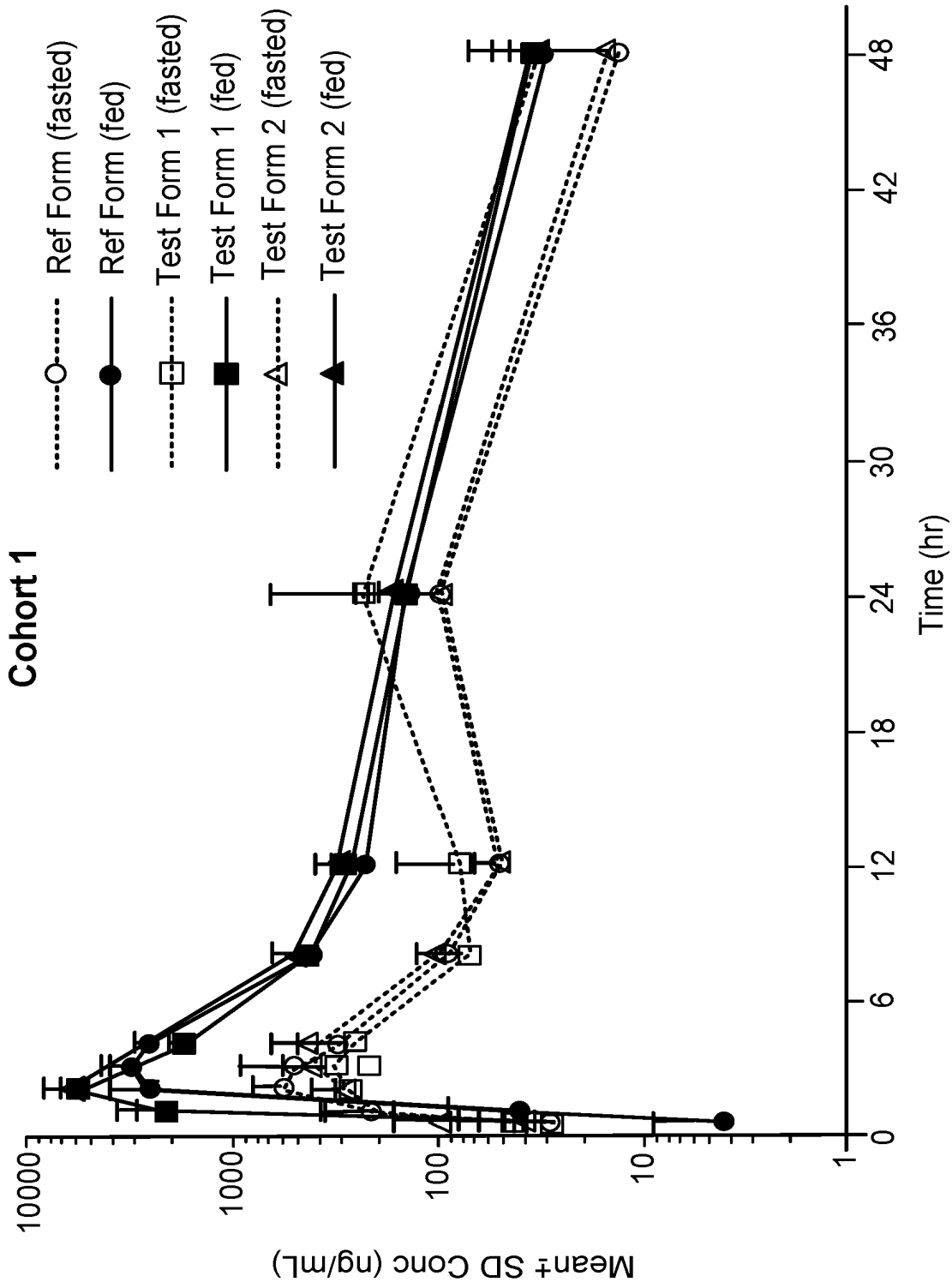

Cohort 1
Ref Form (fasted)
Ref Form (fed)
Test Form 1 (fasted)
Test Form 1 (fed)
Test Form 2 (fasted)
Test Form 2 (fed)
Mean± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6A

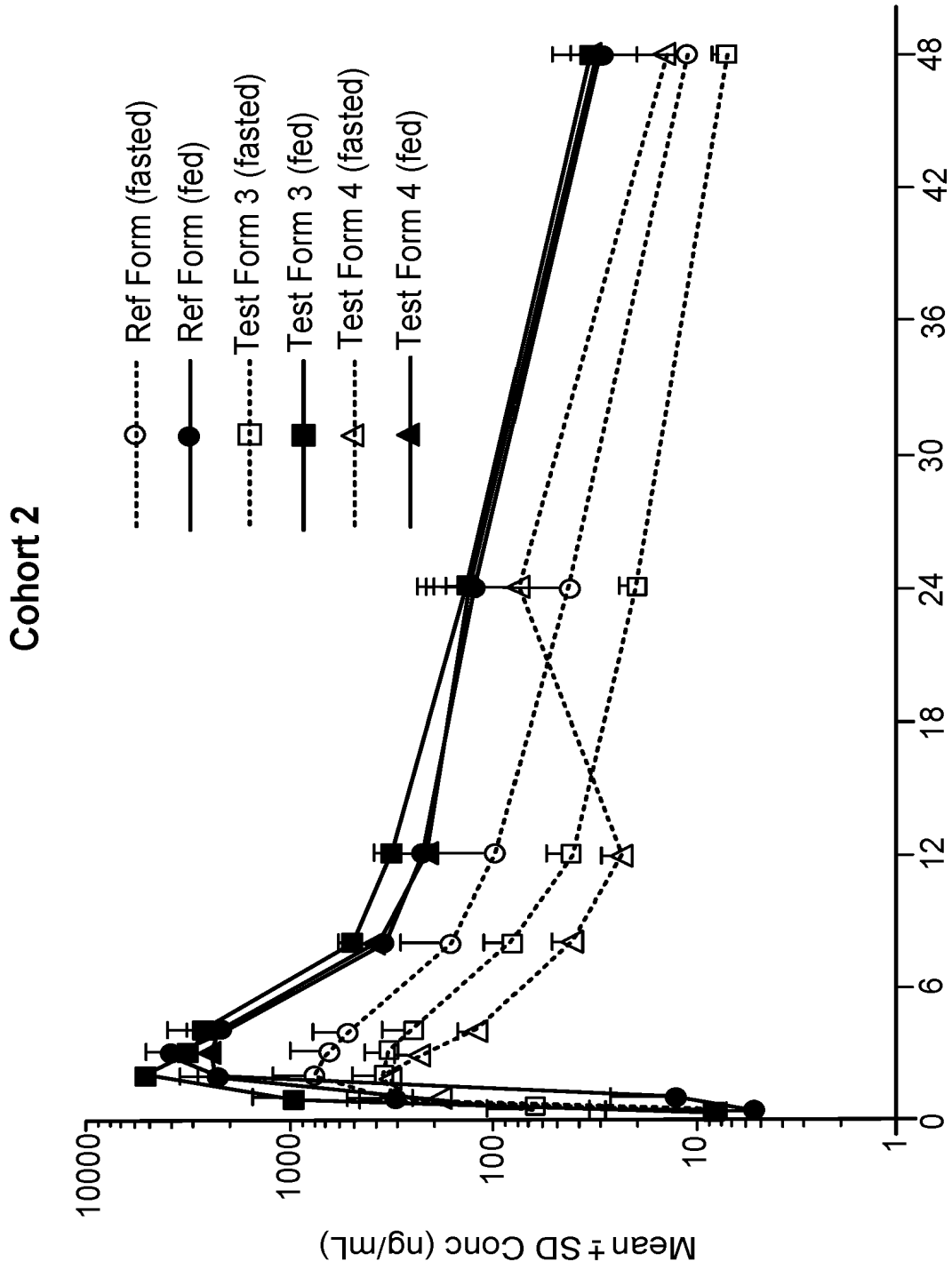

Cohort 2
Ref Form (fasted)
Ref Form (fed)
Test Form 3 (fasted)
Test Form 3 (fed)
Test Form 4 (fasted)
Test Form 4 (fed)
Mean ± SD Conc (ng/mL)
10000
1000
100
10
1
0
6
12
18
24
30
36
42
48
Time (hr)

FIG. 6B

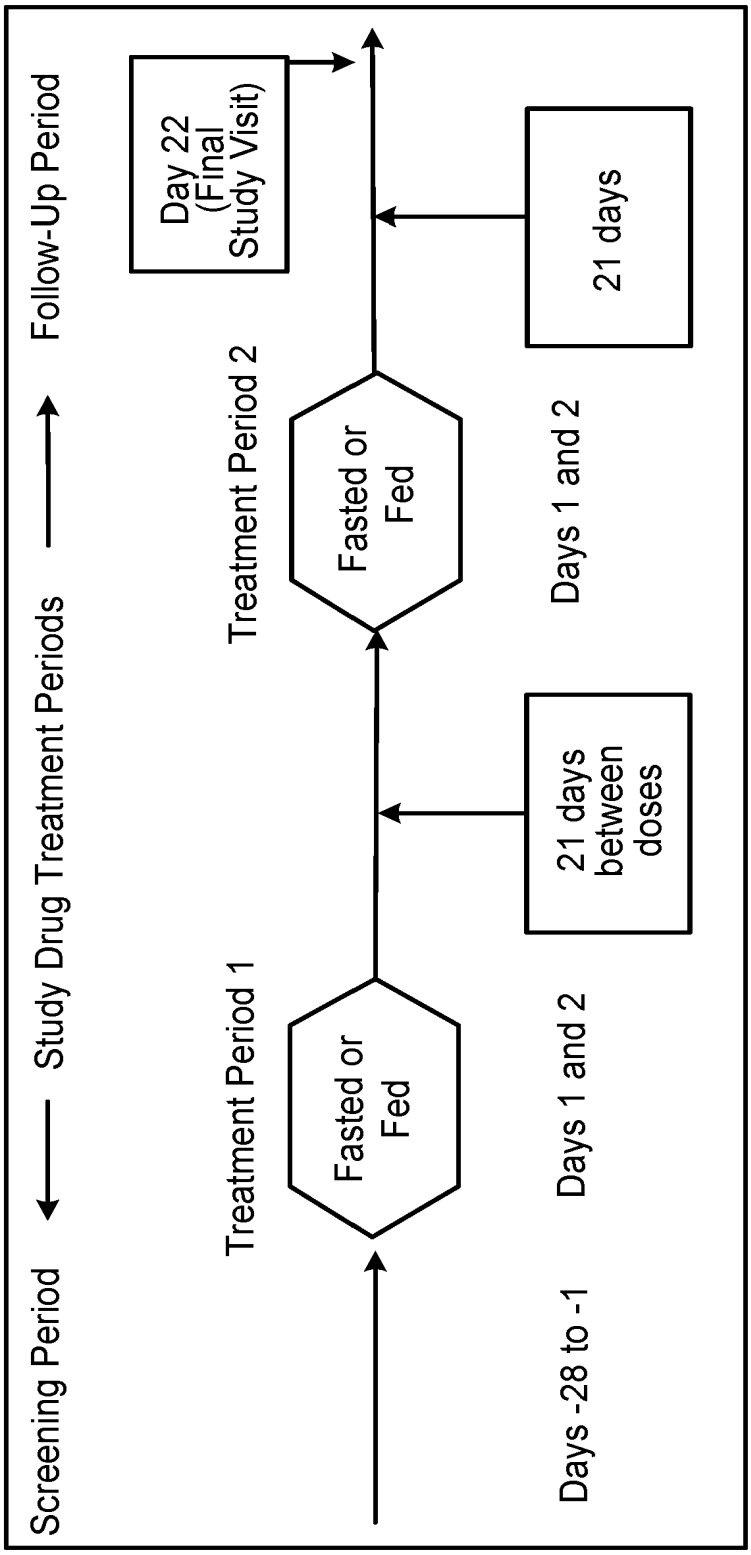

Screening Period
Study Drug Treatment Periods
Follow-Up Period
Days -28 to -1
Treatment Period 1
Fasted or Fed
Days 1 and 2
21 days between doses
Treatment Period 2
Fasted or Fed
Days 1 and 2
21 days
Day 22 (Final Study Visit)

FIG. 7

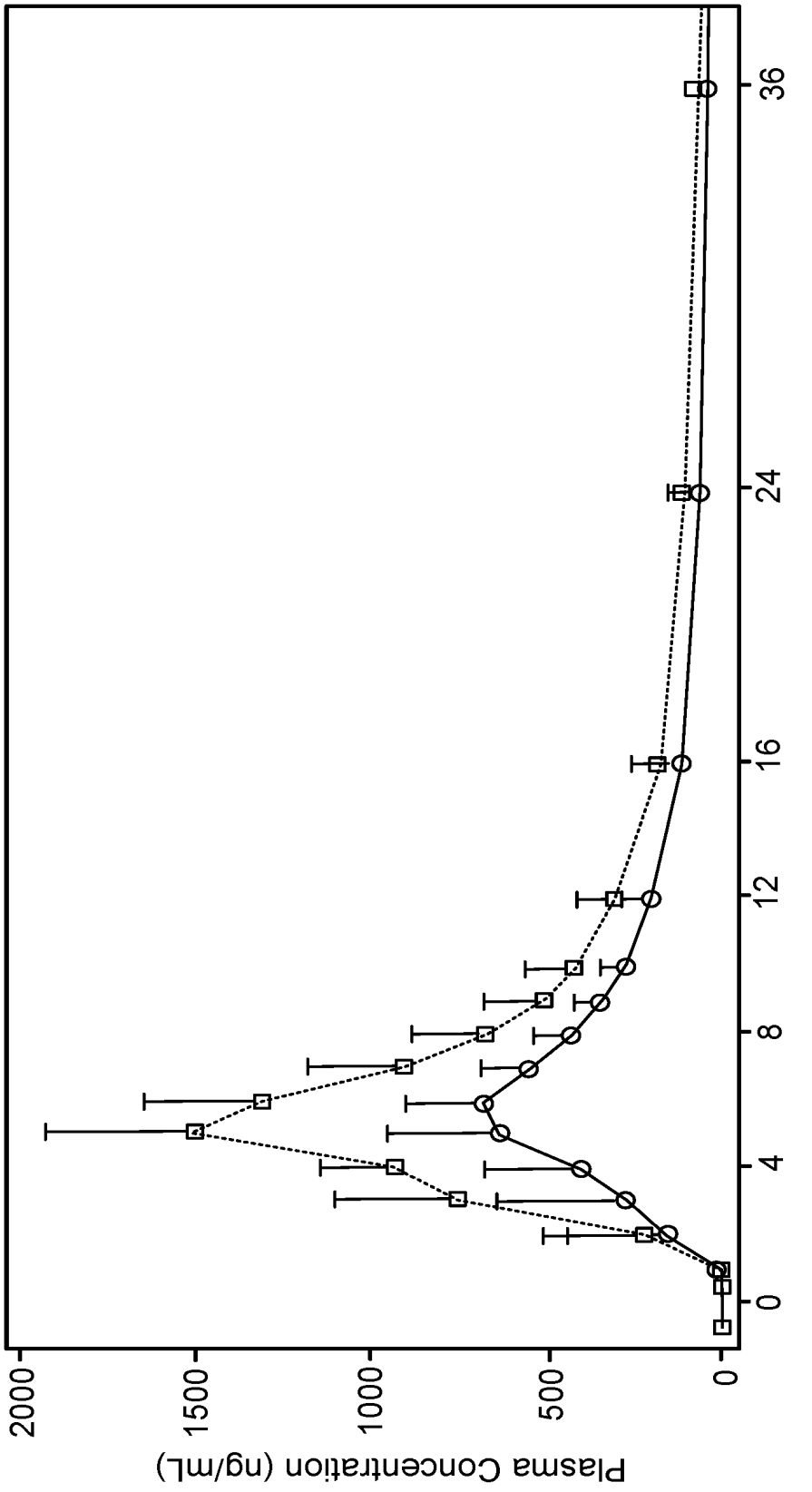

Plasma Concentration (ng/mL)
2000
1500
1000
500
0
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8A

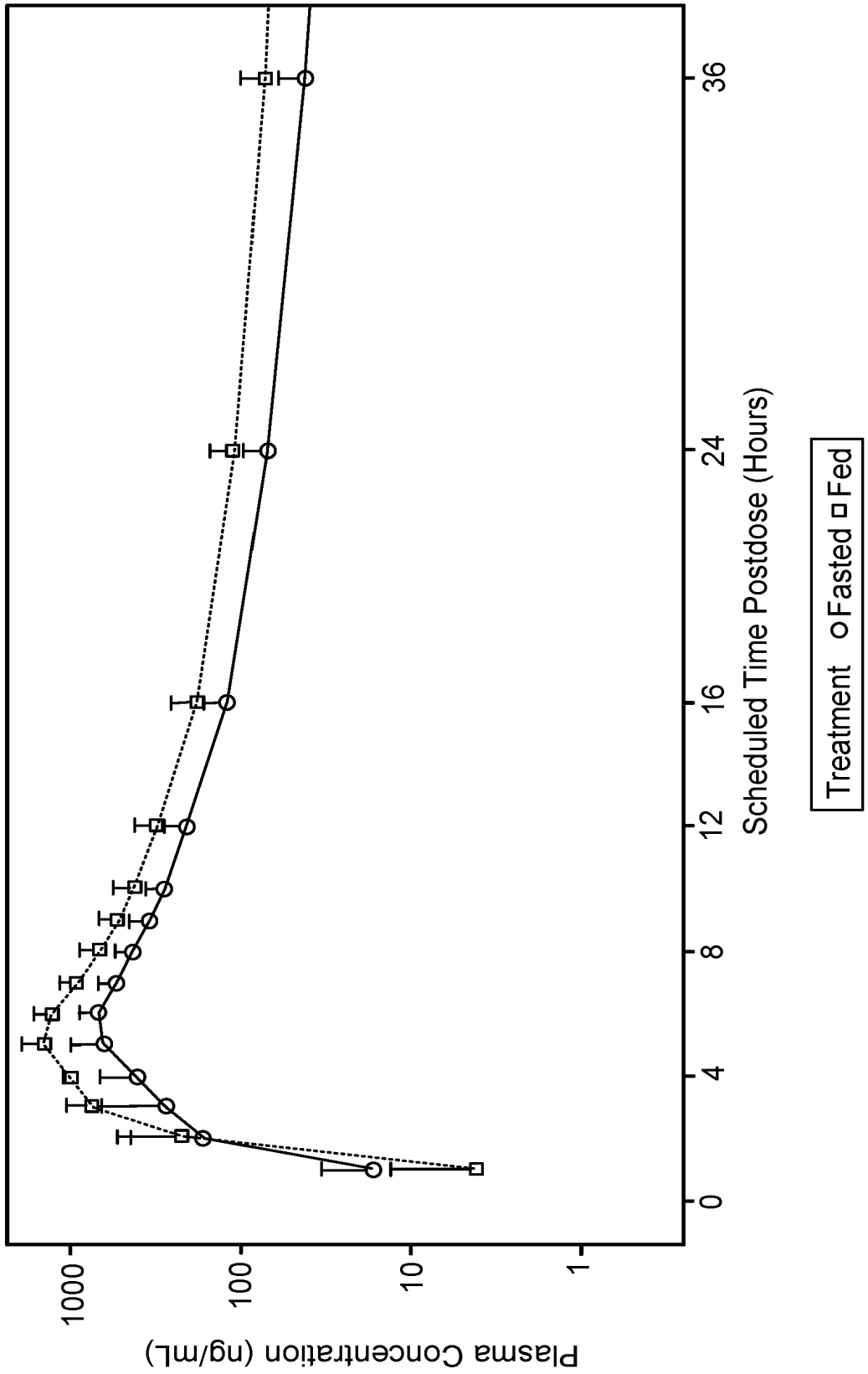

Plasma Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
24
36
Scheduled Time Postdose (Hours)
Treatment Fasted Fed

FIG. 8B

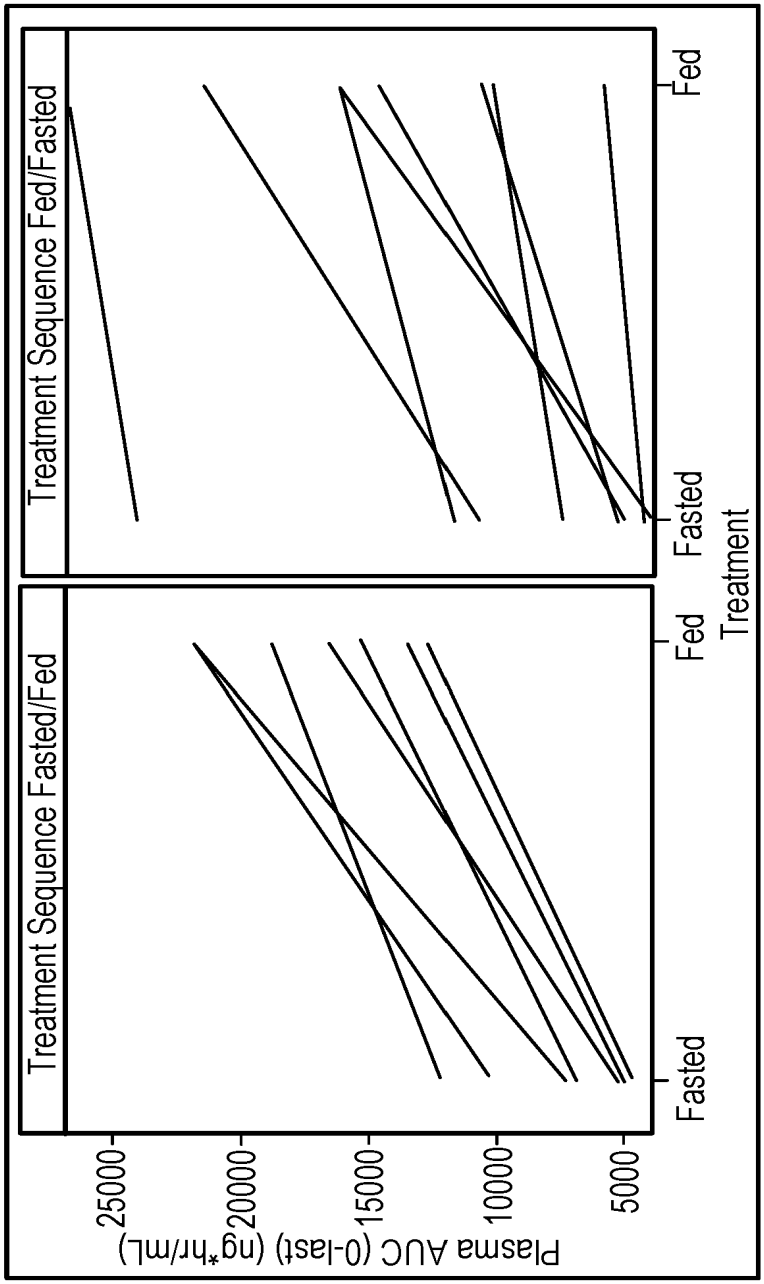

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9A

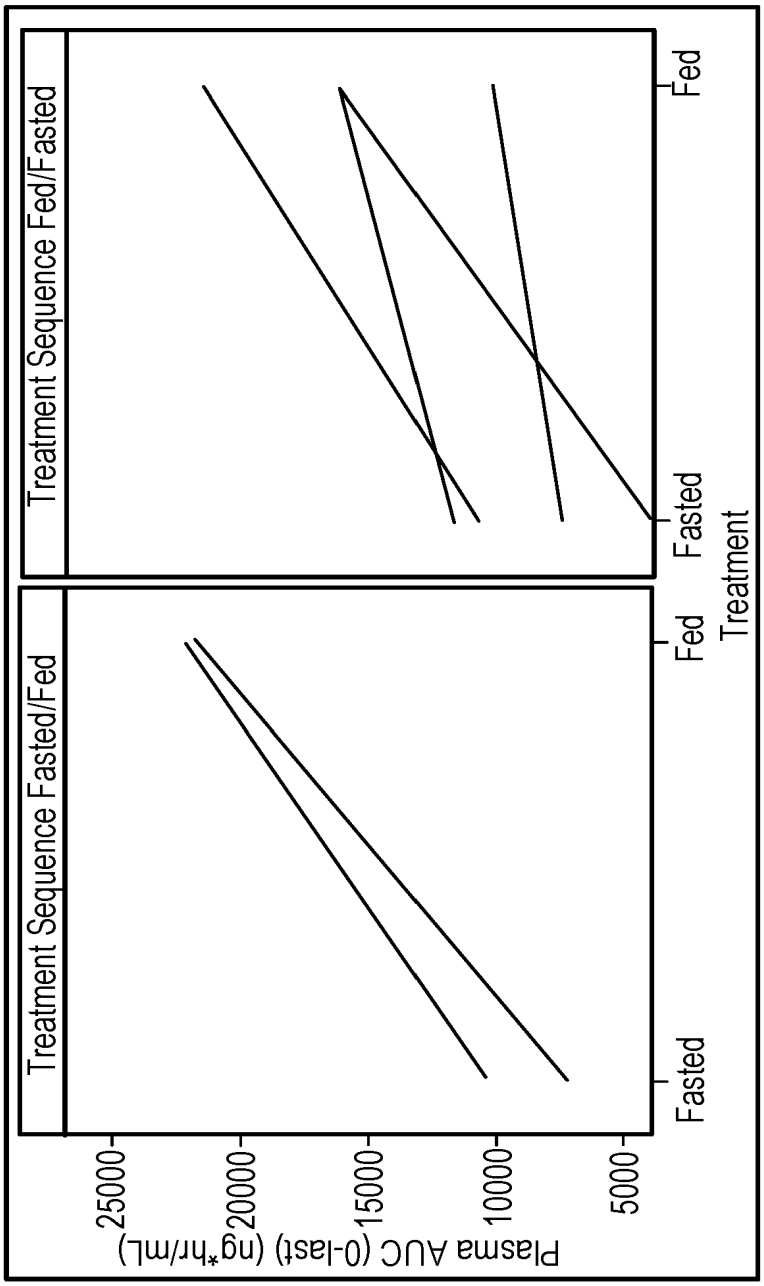

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma AUC (0-last) (ng*hr/mL)
25000
20000
15000
10000
5000
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9B

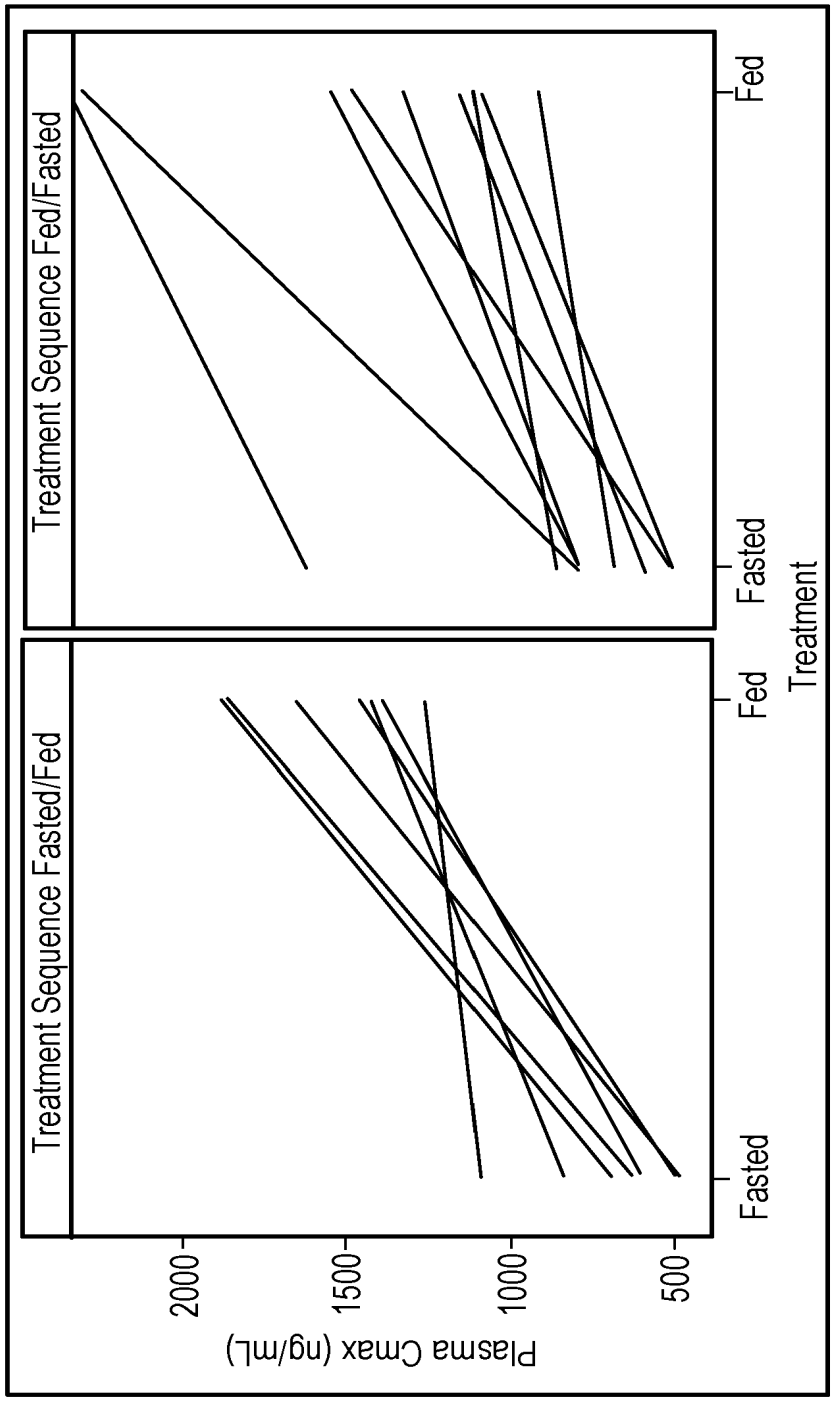
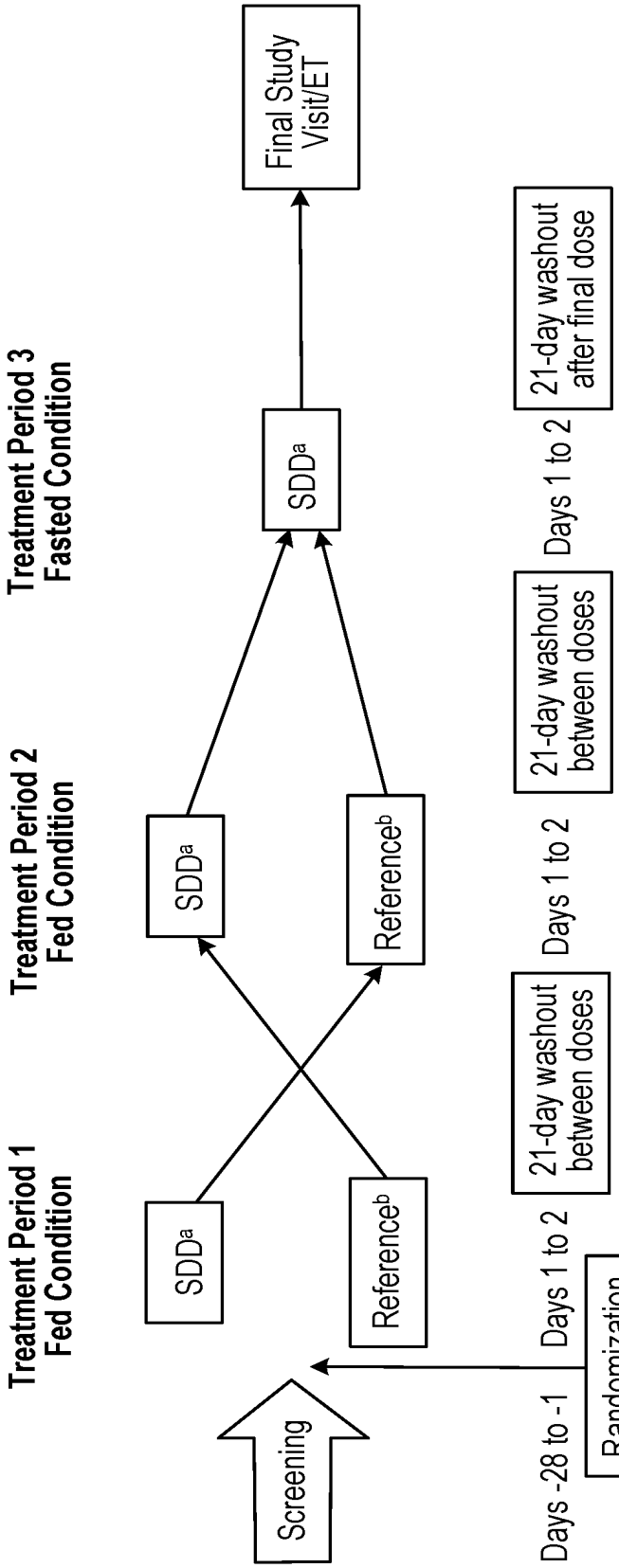

Treatment Sequence Fasted/Fed
Treatment Sequence Fed/Fasted
Plasma Cmax (ng/mL)
2000
1500
1000
500
Fasted
Fed
Fed
Fasted
Treatment

FIG. 9C



a SDD=Compound of Formula (I) spray dried dispersion (suspension or capsule formulation).
b Reference formulation=Compound of Formula (I) encapsulated, lipid semi-solid.

FIG. 10

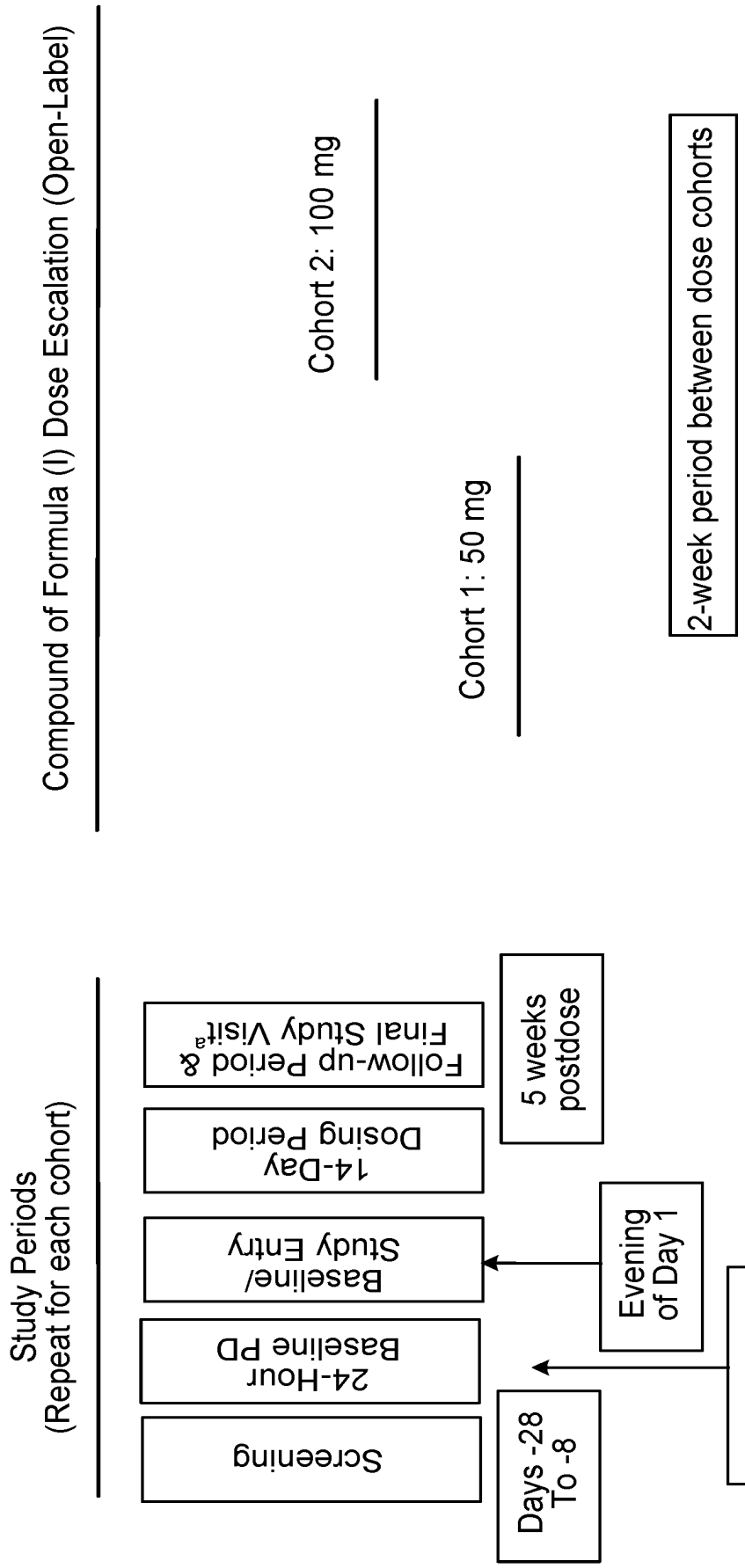


FIG. 11

a Visit on Days 21 (+3 days), 28 (+3 days), and 35 (+3 days); final study visit on Day 49 (+7 days) or early termination.
PD = pharmacodynamic.

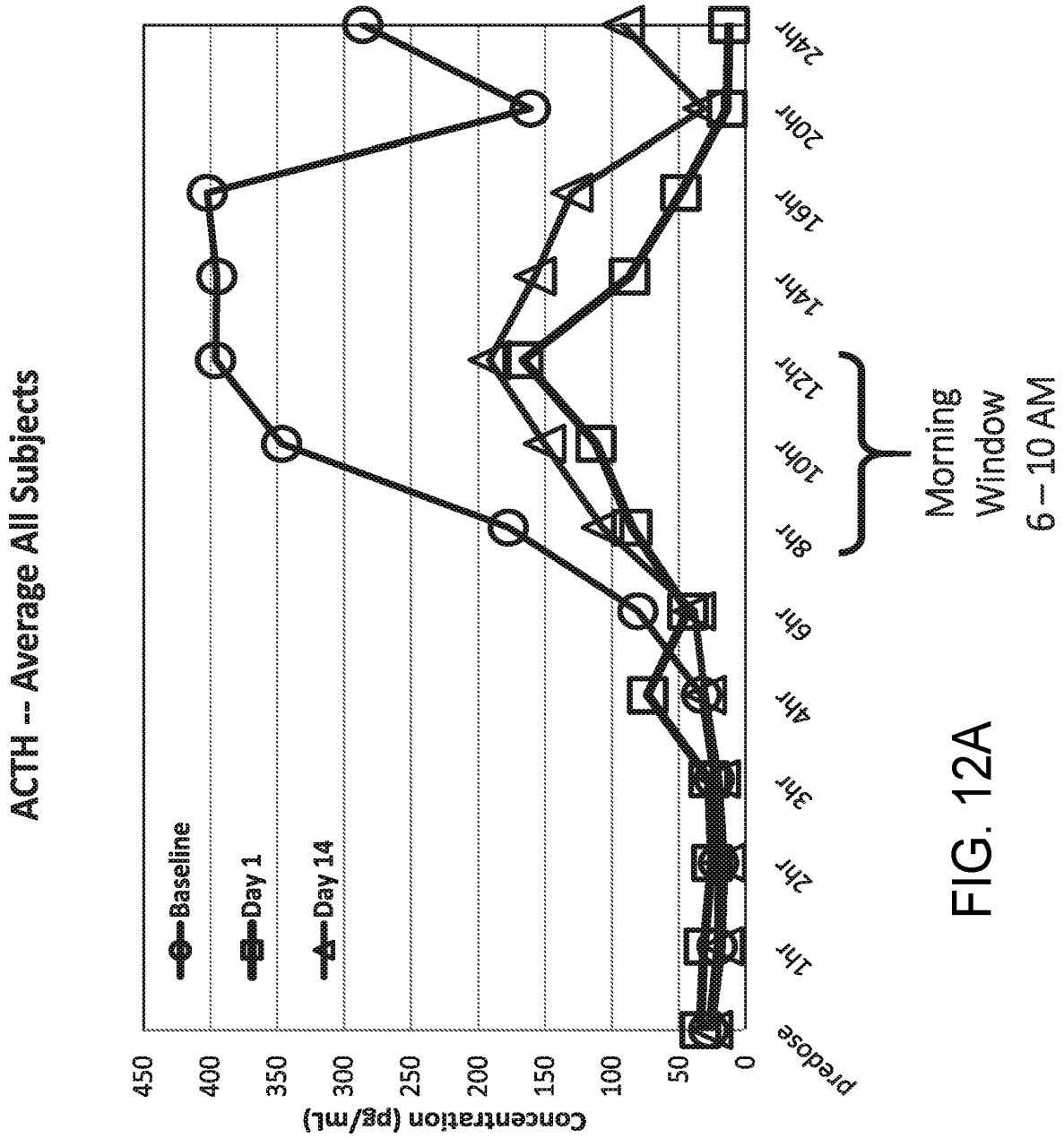

ACTH -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
450
400
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12A

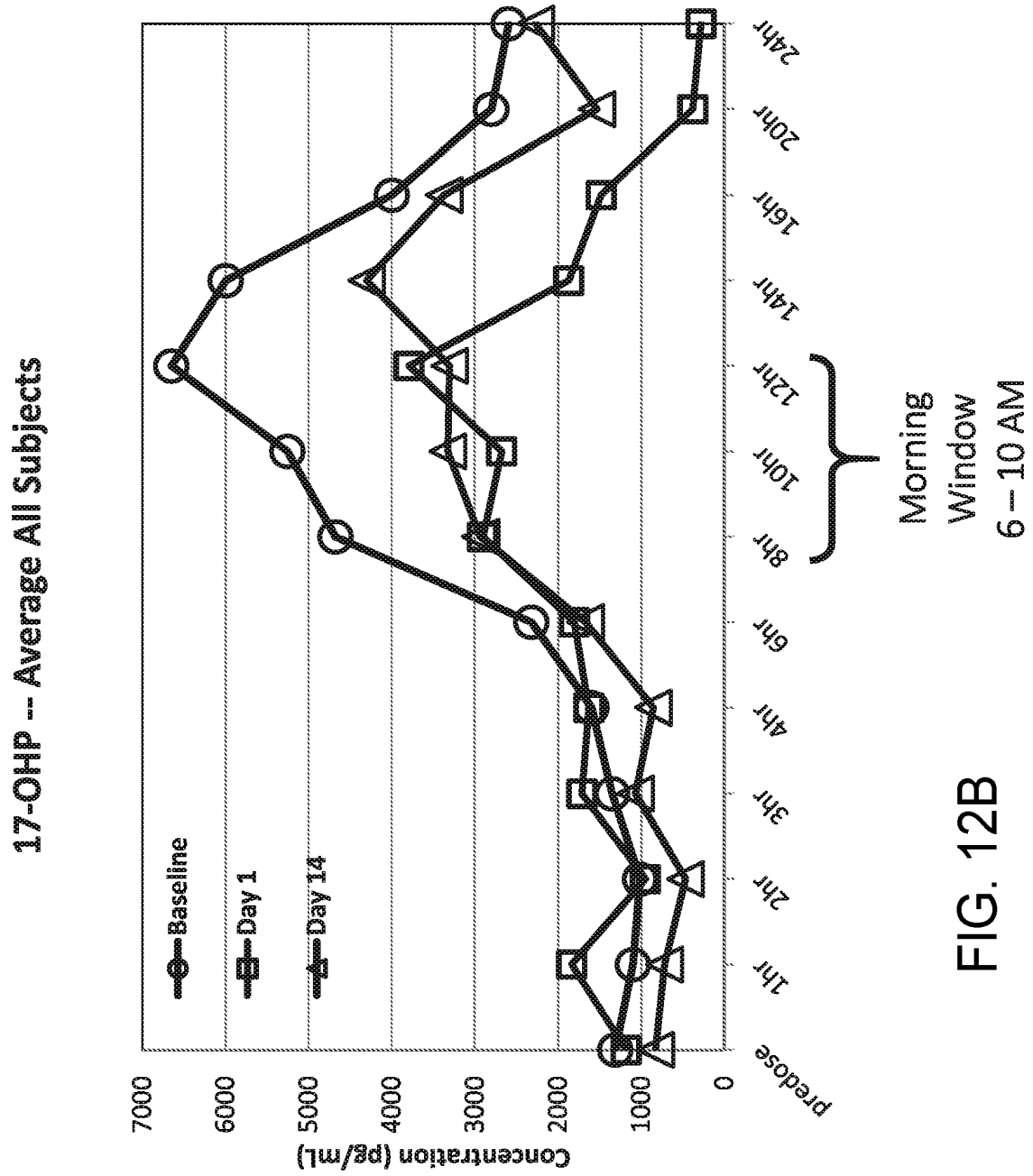

17-OHP -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 12B

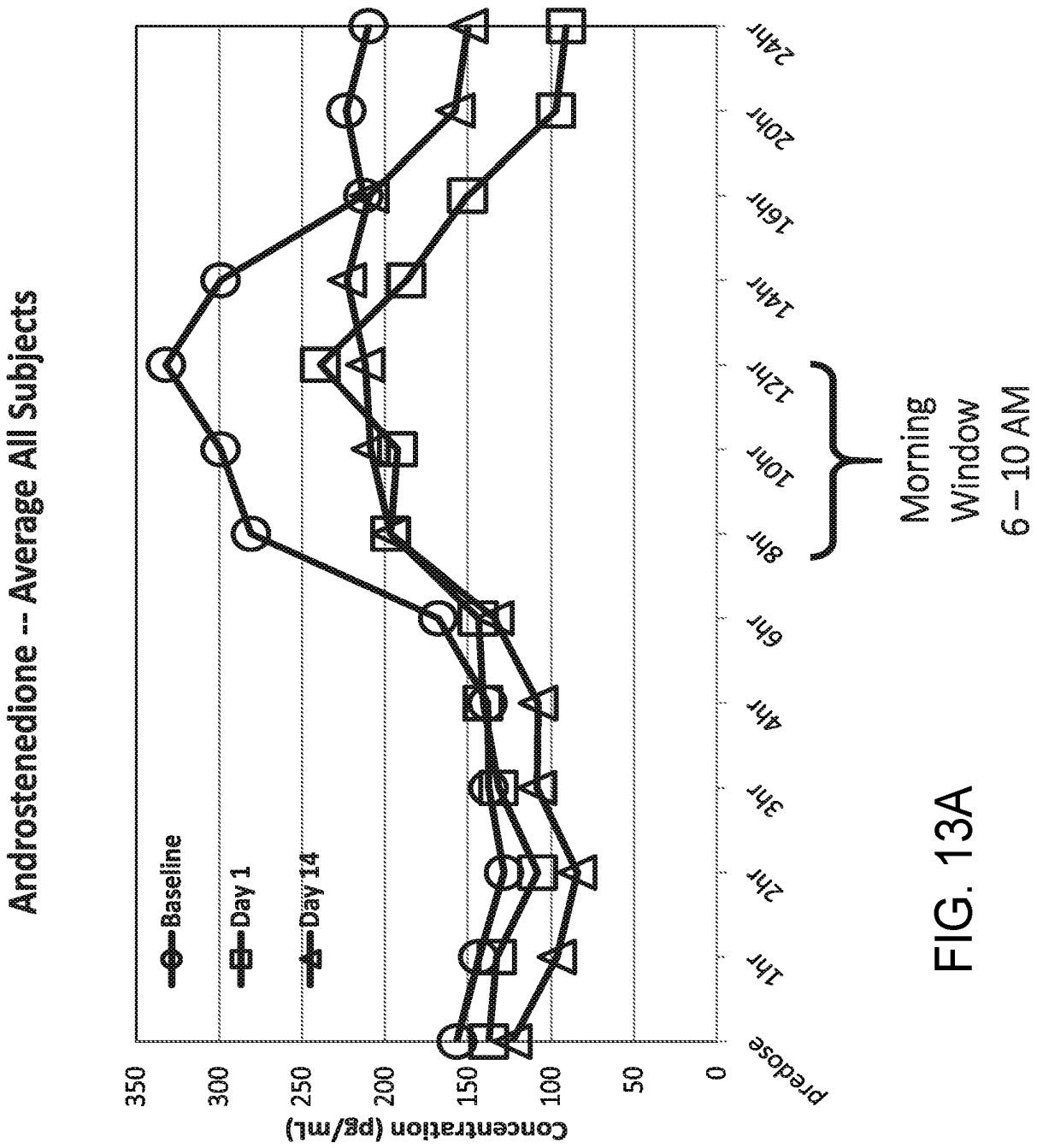

Androstenedione -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
350
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13A

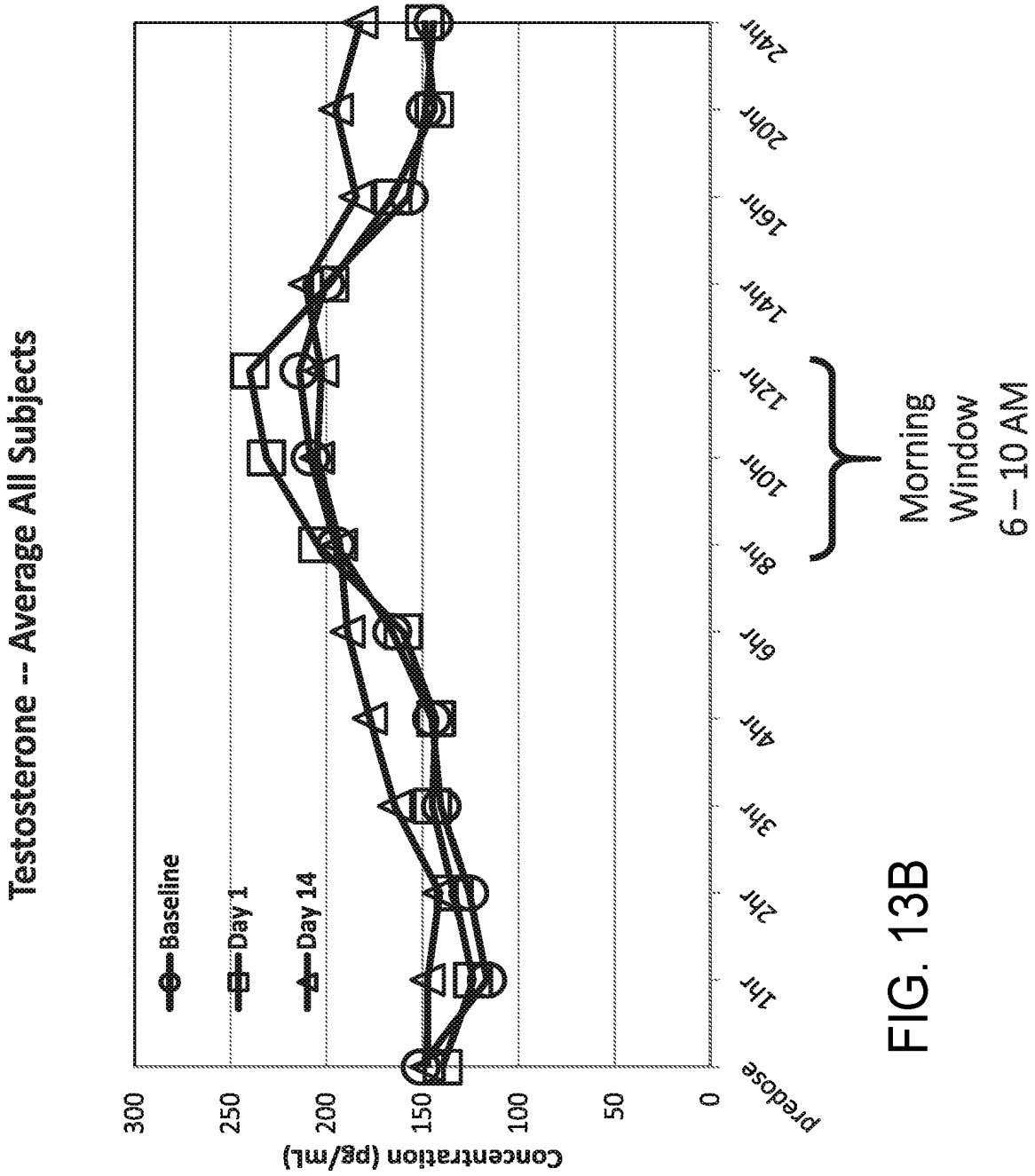

Testosterone -- Average All Subjects
Baseline
Day 1
Day 14
Concentration (pg/mL)
300
250
200
150
100
50
0
predose
1hr
2hr
3hr
4hr
6hr
8hr
10hr
12hr
14hr
16hr
20hr
24hr
Morning
Window
6 – 10 AM

FIG. 13B

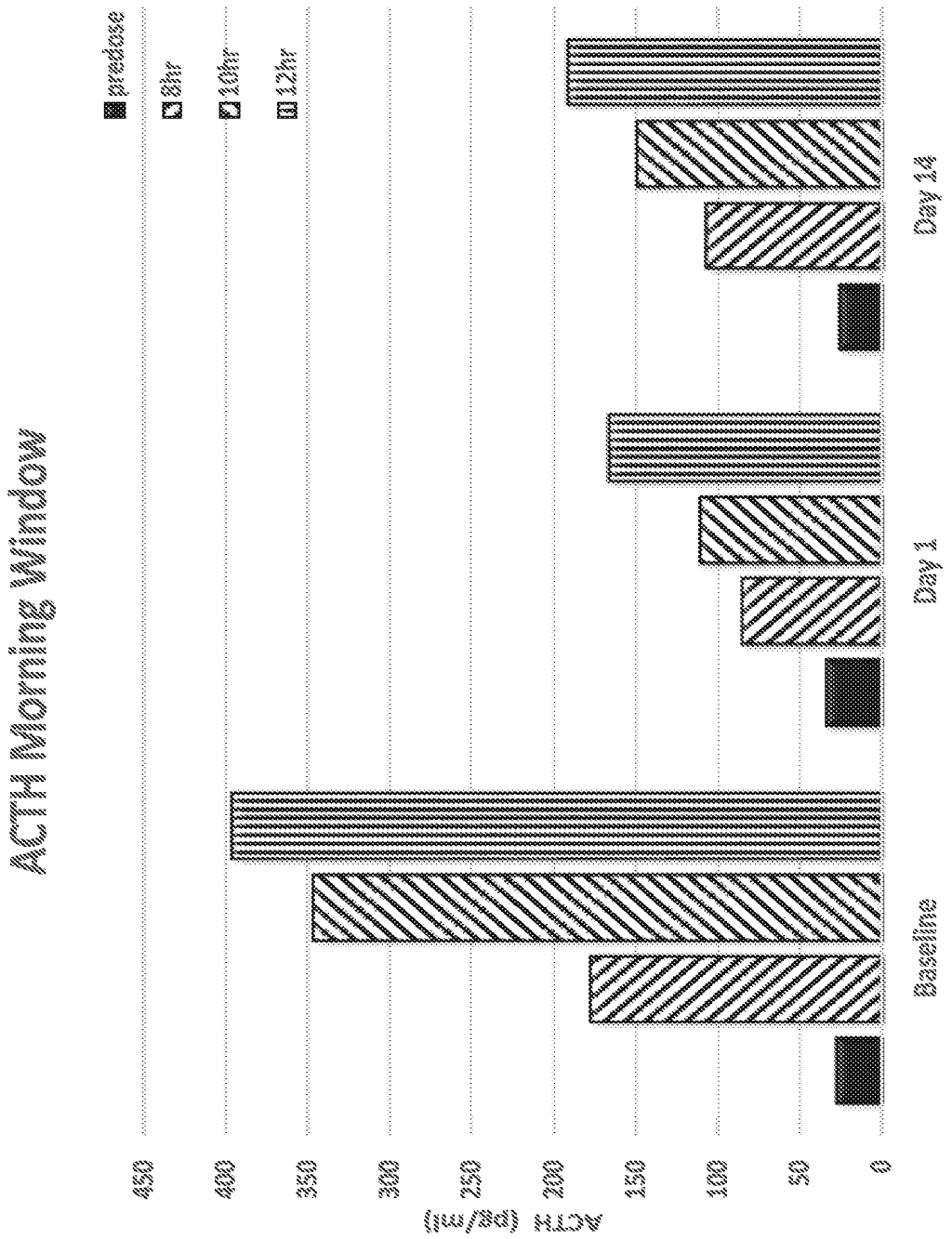

predose
8hr
10hr
12hr
ACTH Morning Window
ACTH (pg/ml)
450
400
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14A

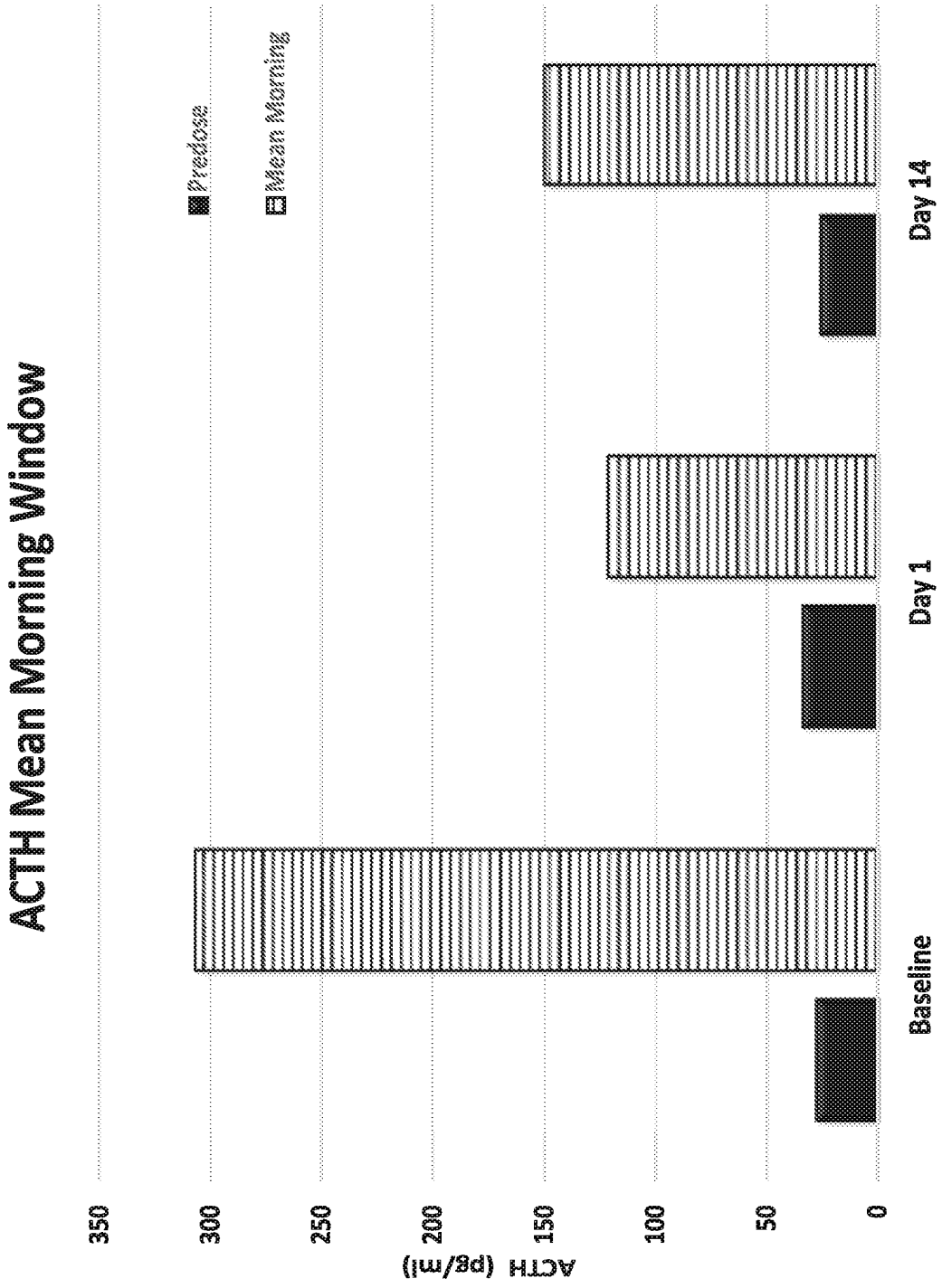

ACTH Mean Morning Window
Predose
Mean Morning
ACTH (pg/ml)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 14B

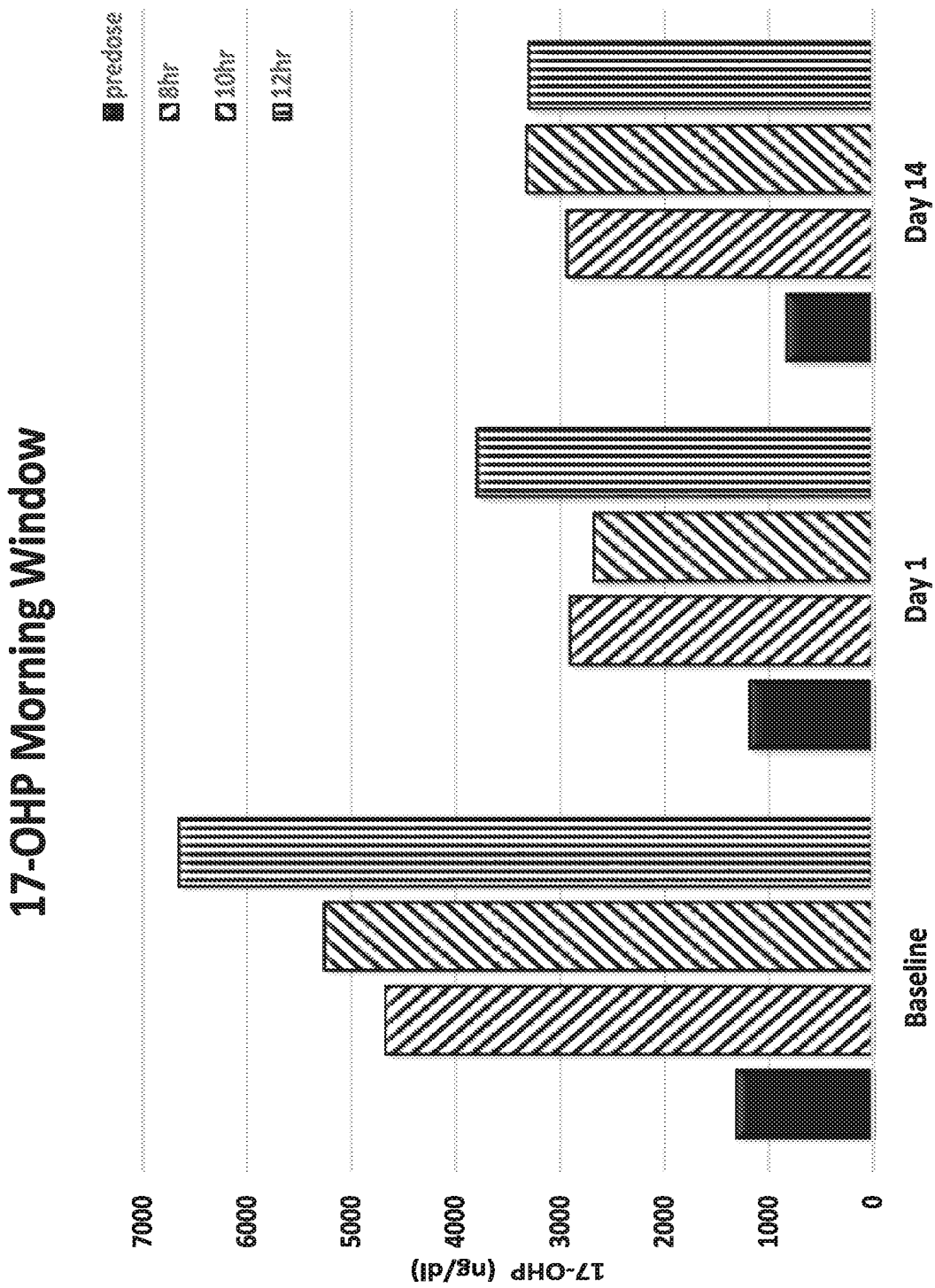

17-OHP Morning Window
predose
8hr
10hr
12hr
17-OHP (ng/dl)
7000
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15A

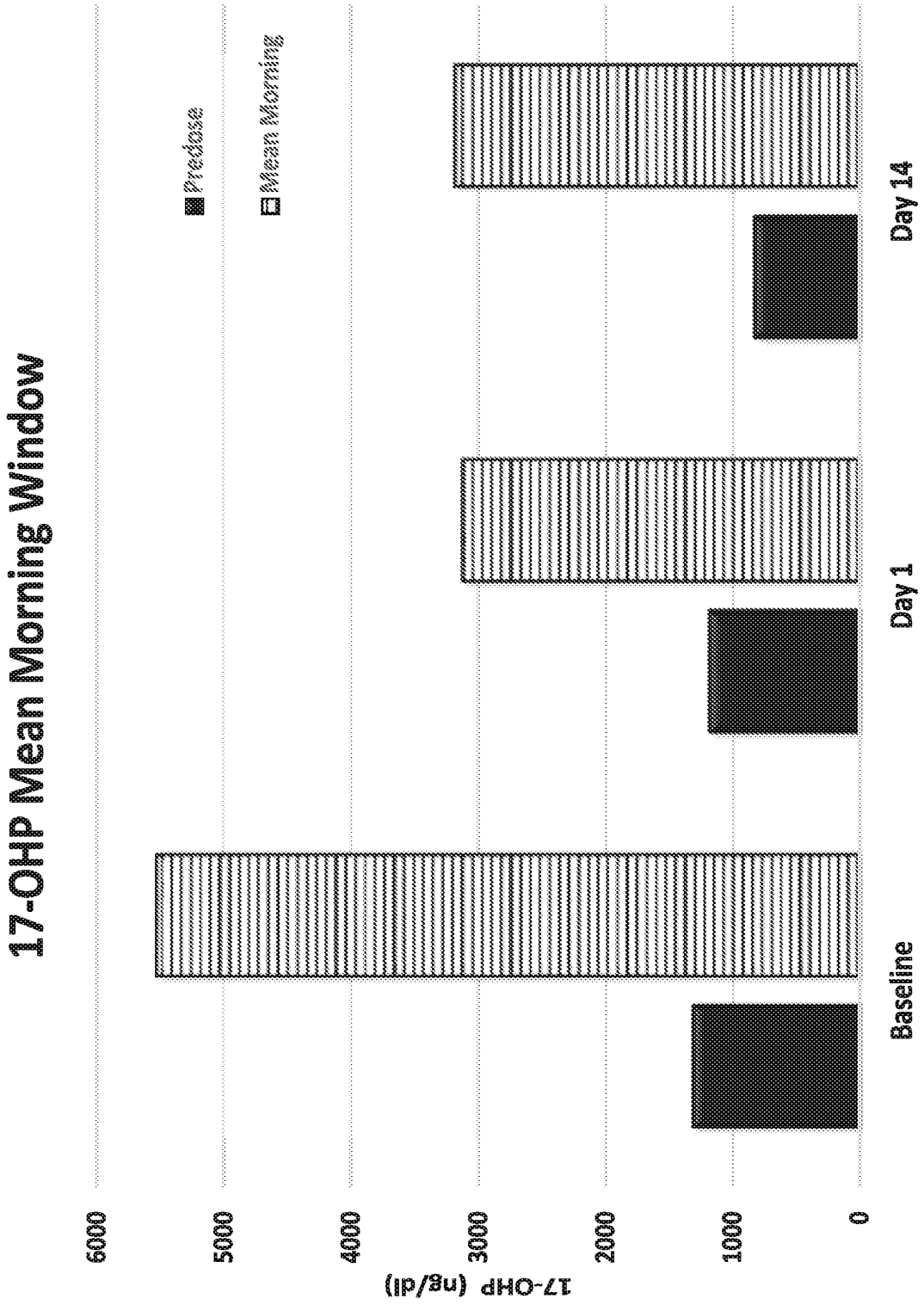

17-OHP Mean Morning Window
Predose
Mean Morning
17-OHP (ng/dl)
6000
5000
4000
3000
2000
1000
0
Baseline
Day 1
Day 14

FIG. 15B

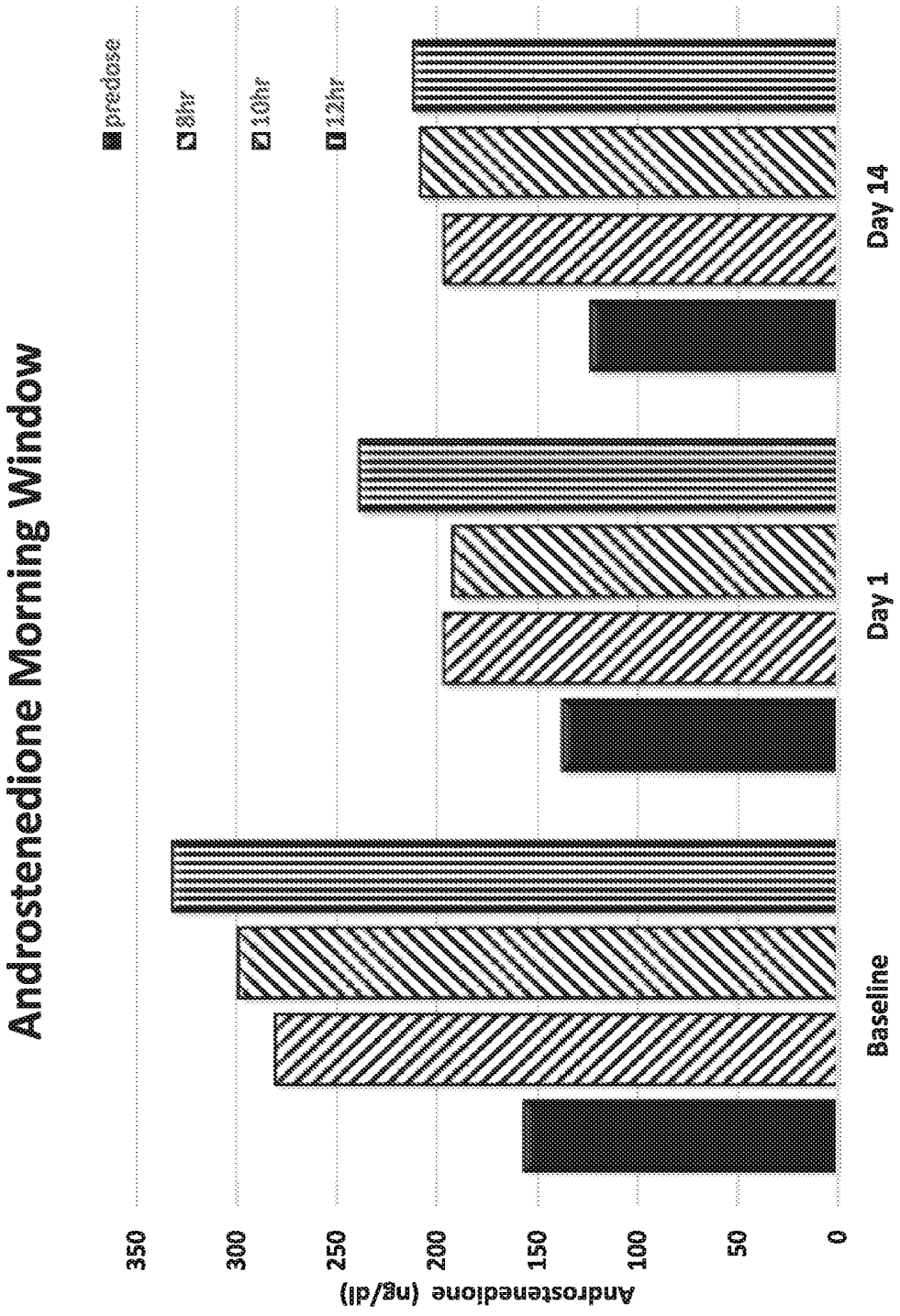

Androstenedione Morning Window
predose
8hr
10hr
12hr
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16A

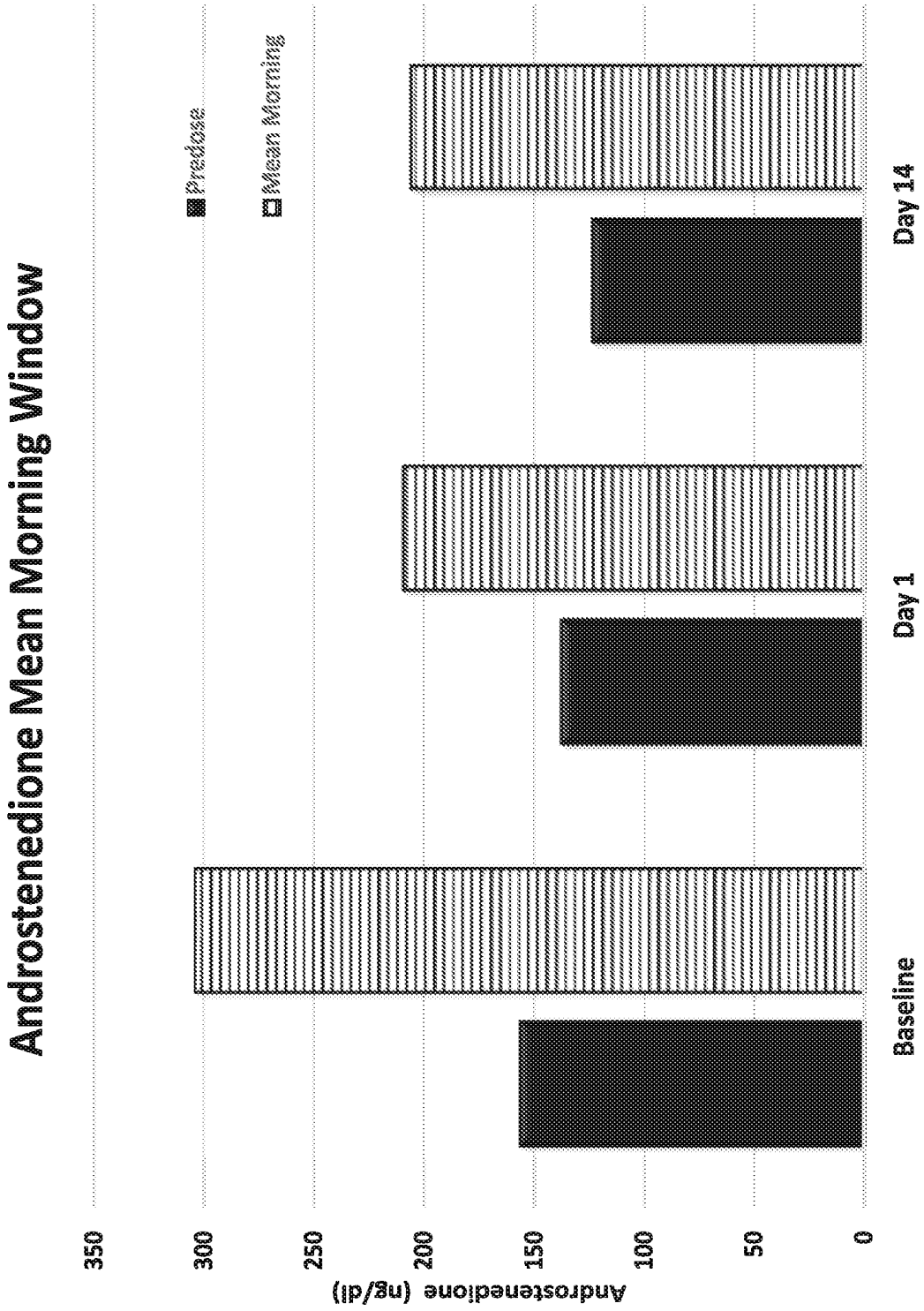

Androstenedione Mean Morning Window
Predose
Mean Morning
Androstenedione (ng/dl)
350
300
250
200
150
100
50
0
Baseline
Day 1
Day 14

FIG. 16B

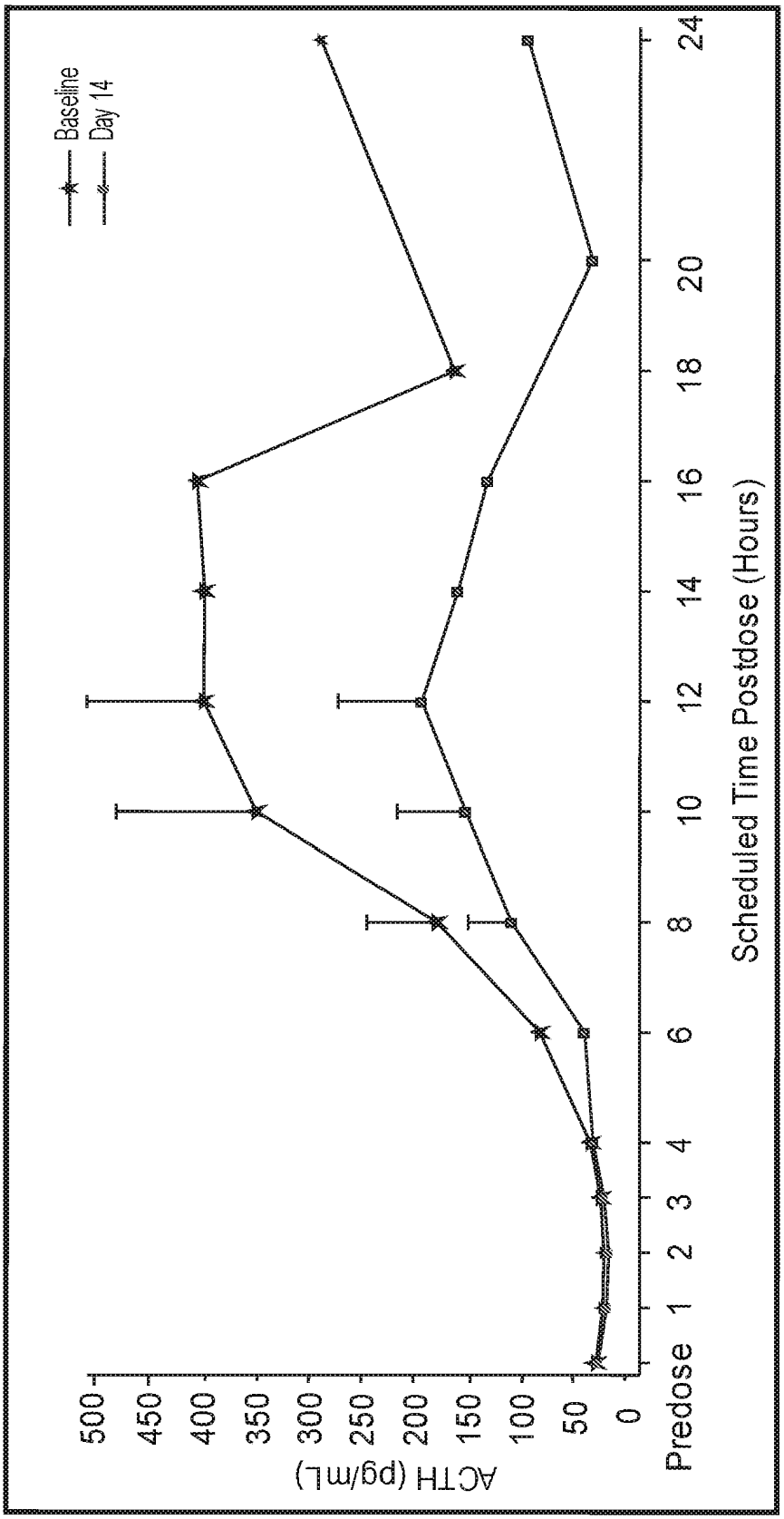

Baseline
Day 14
ACTH (pg/mL)
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17A

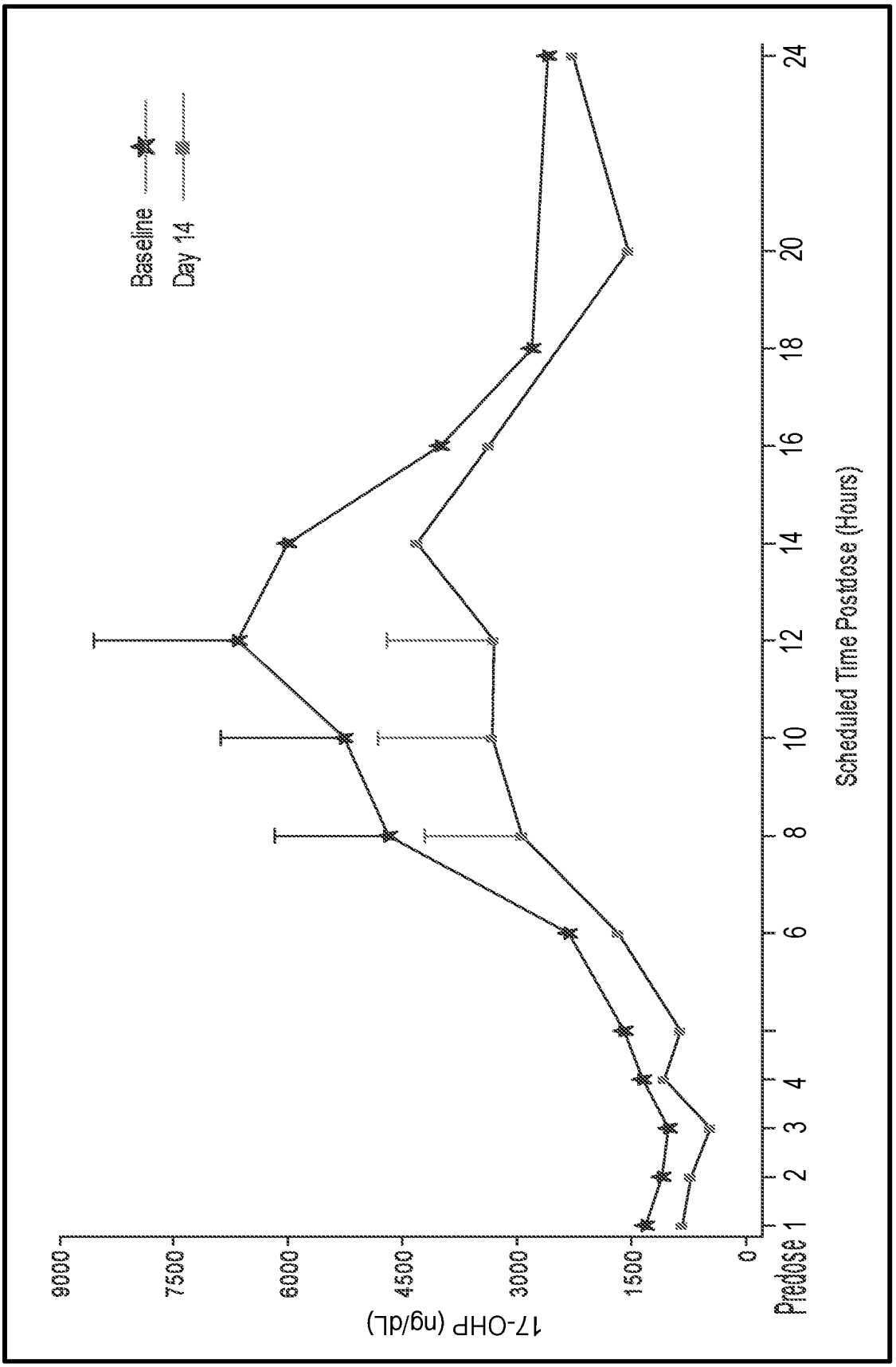

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 17B

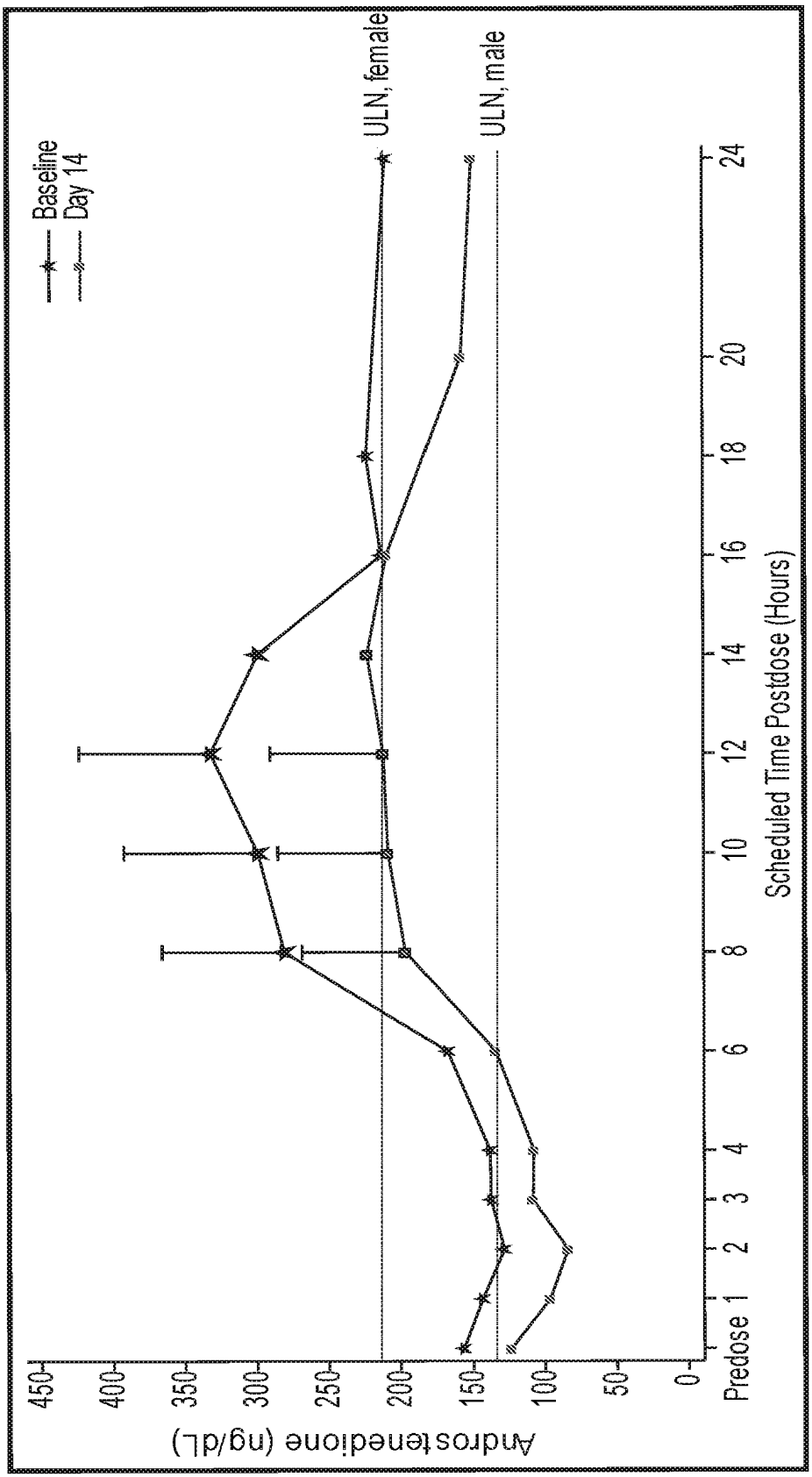

Androstenedione (ng/dL)
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)
ULN, female
ULN, male
Baseline
Day 14

FIG. 17C

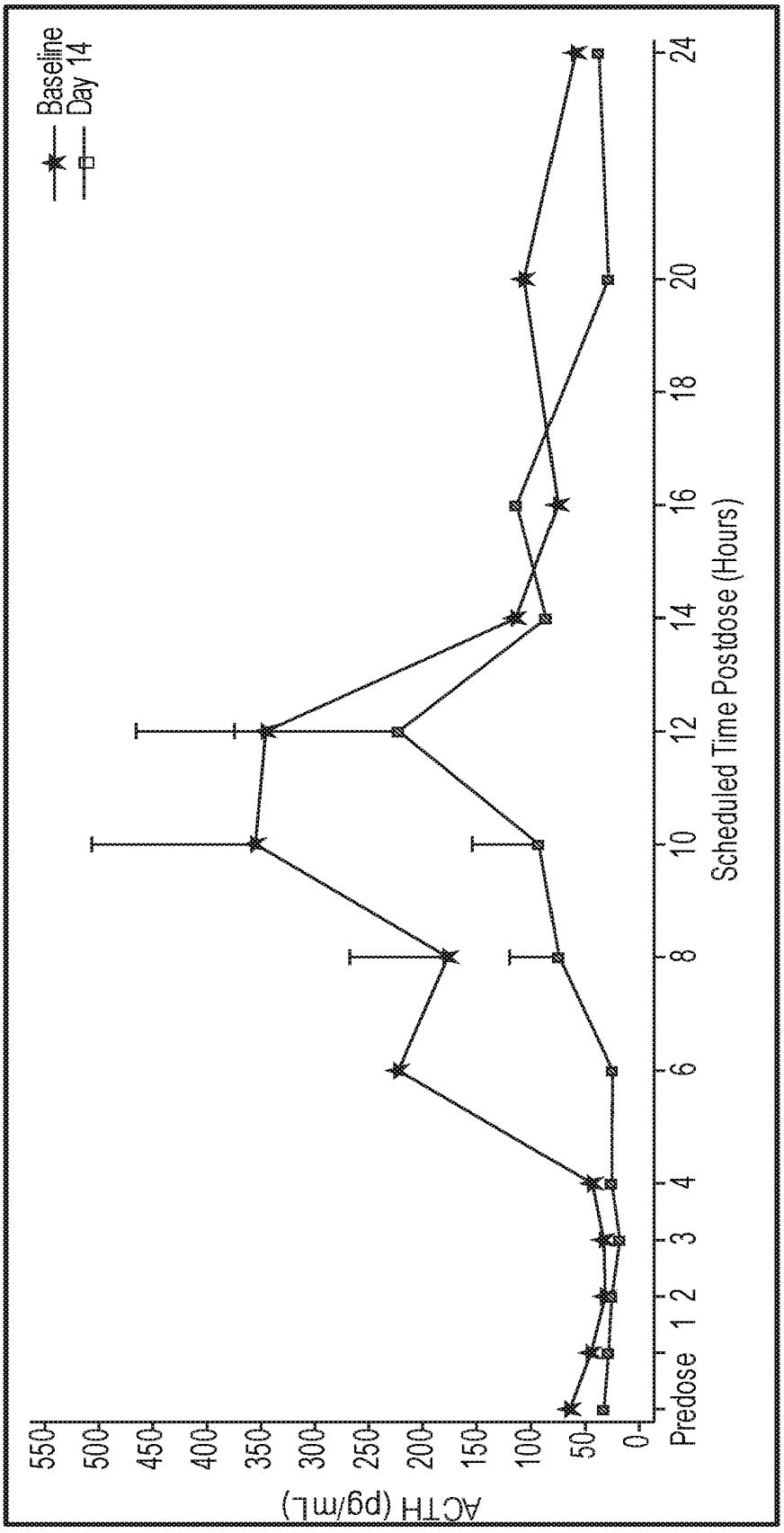

Baseline
Day 14
ACTH (pg/mL)
550
500
450
400
350
300
250
200
150
100
50
0
Predose
1
2
3
4
6
8
10
12
14
16
18
20
24
Scheduled Time Postdose (Hours)

FIG. 18A

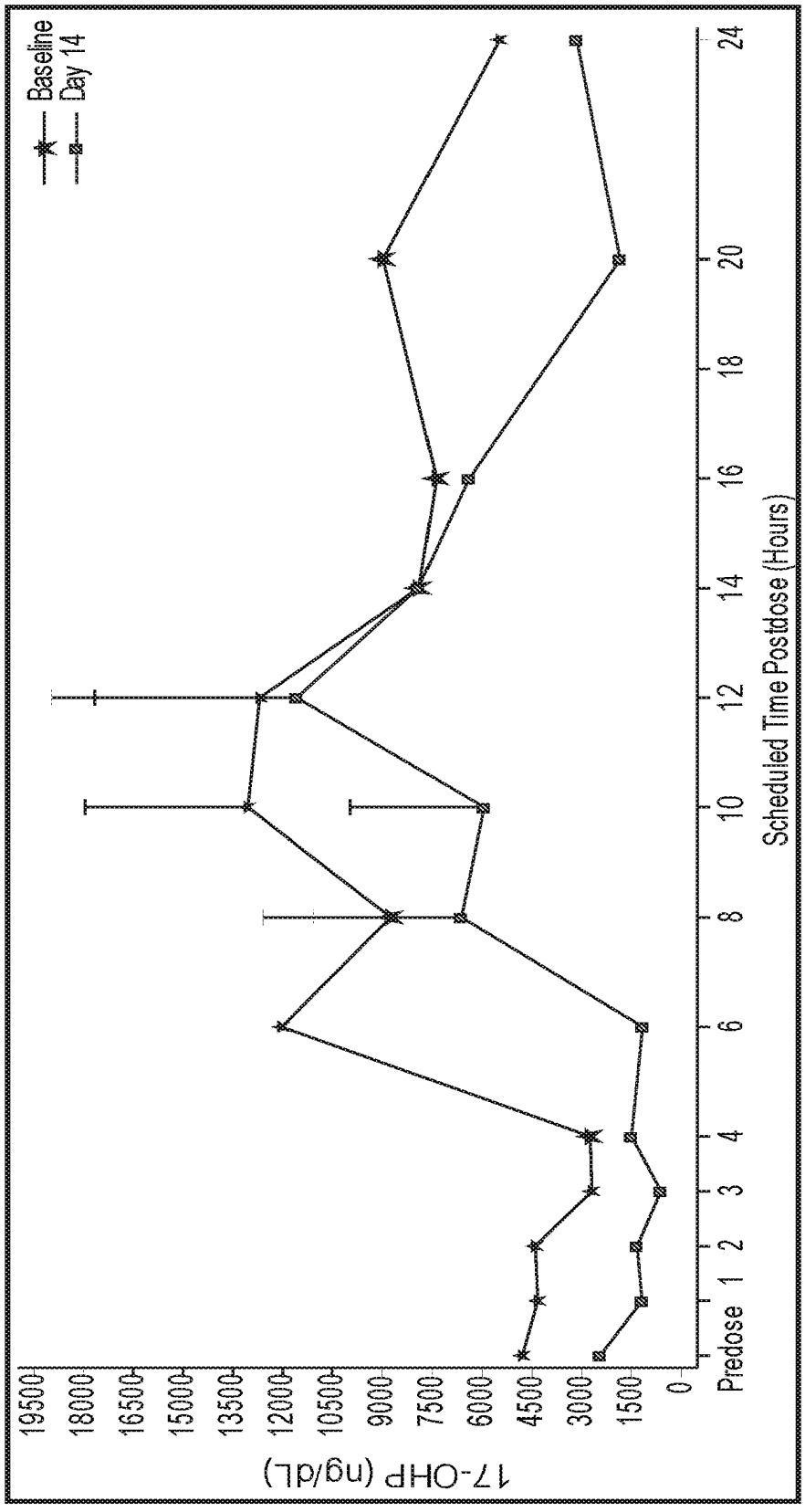

Baseline
Day 14
17-OHP (ng/dL)
19500
18000
16500
15000
13500
12000
10500
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)

FIG. 18B

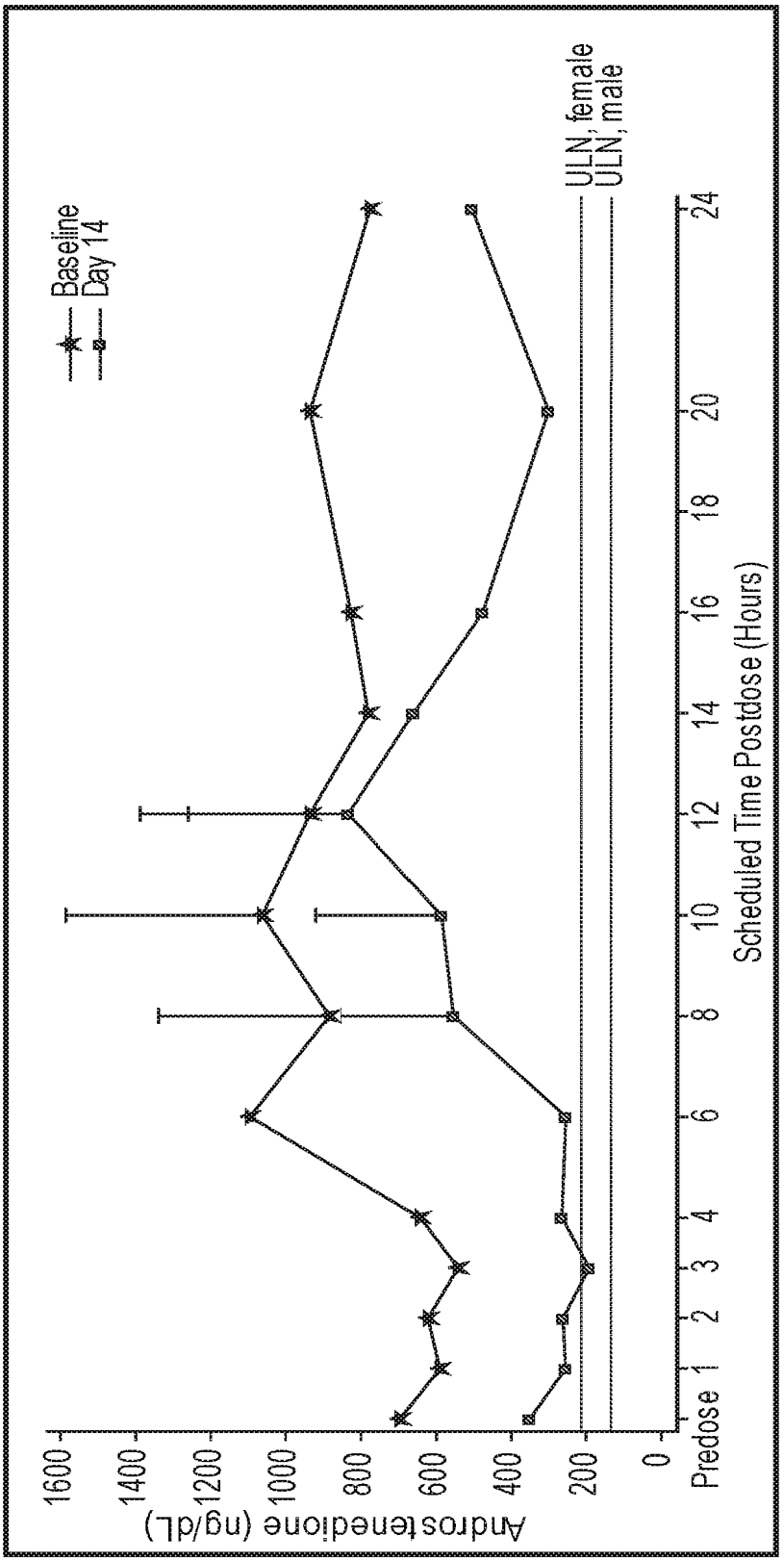

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
1600
1400
1200
1000
800
600
400
200
0
Predose 1 2 3 4 6 8 10 12 14 16 18 20 24
Scheduled Time Postdose (Hours)

FIG. 18C

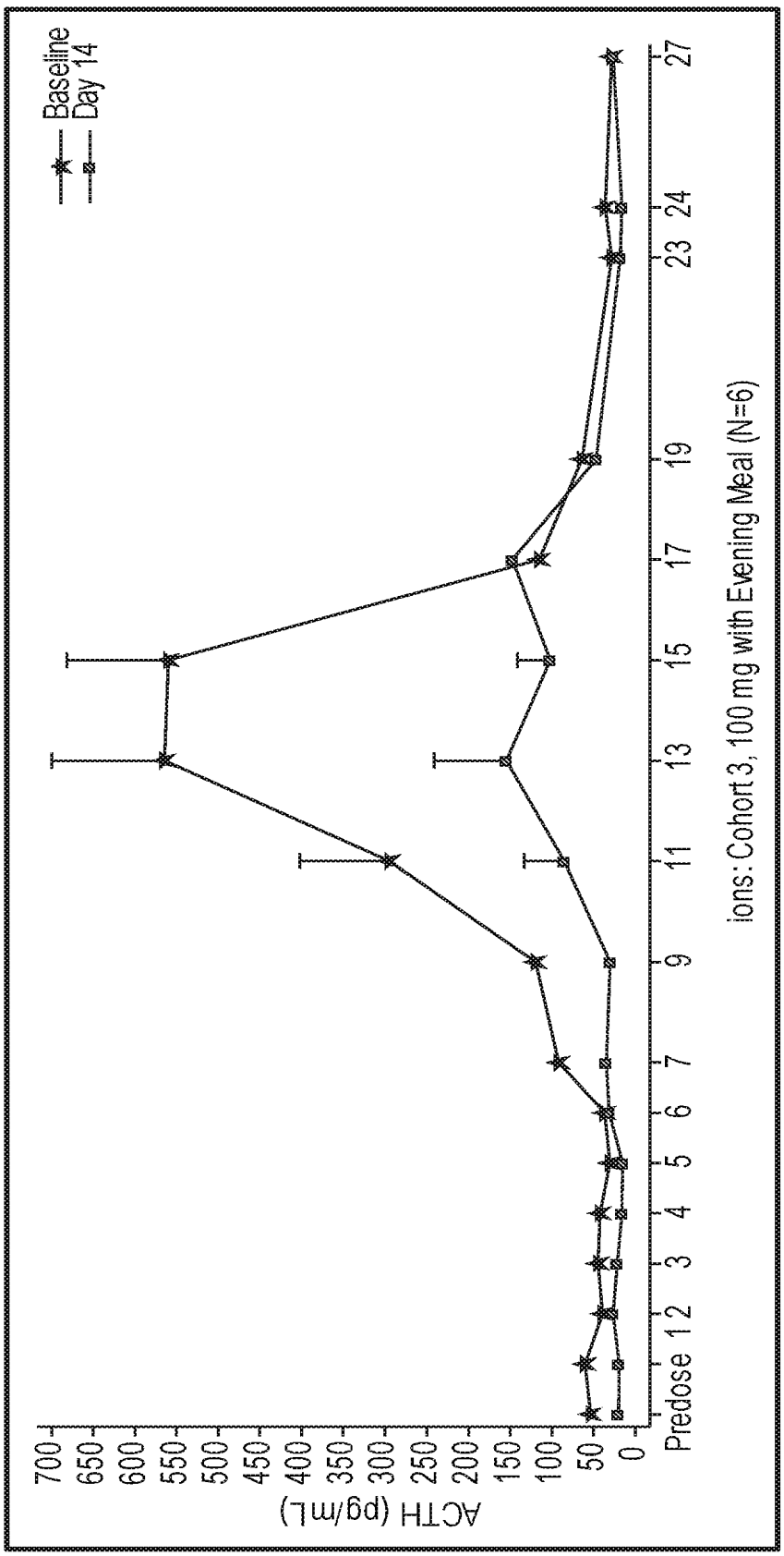

Baseline
Day 14
ACTH (pg/mL)
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
ions: Cohort 3, 100 mg with Evening Meal (N=6)

FIG. 19A

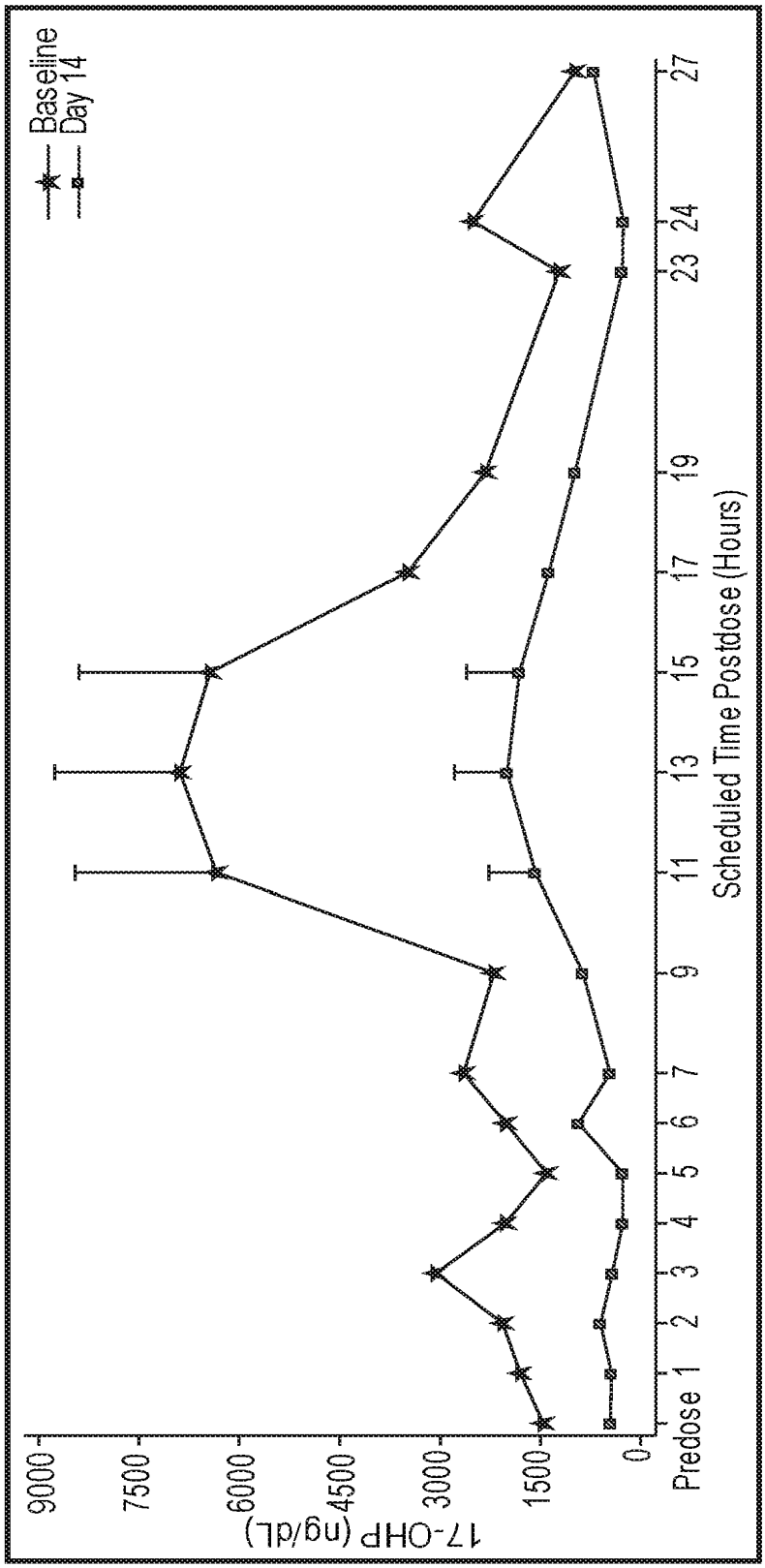

Baseline
Day 14
17-OHP (ng/dL)
9000
7500
6000
4500
3000
1500
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19B

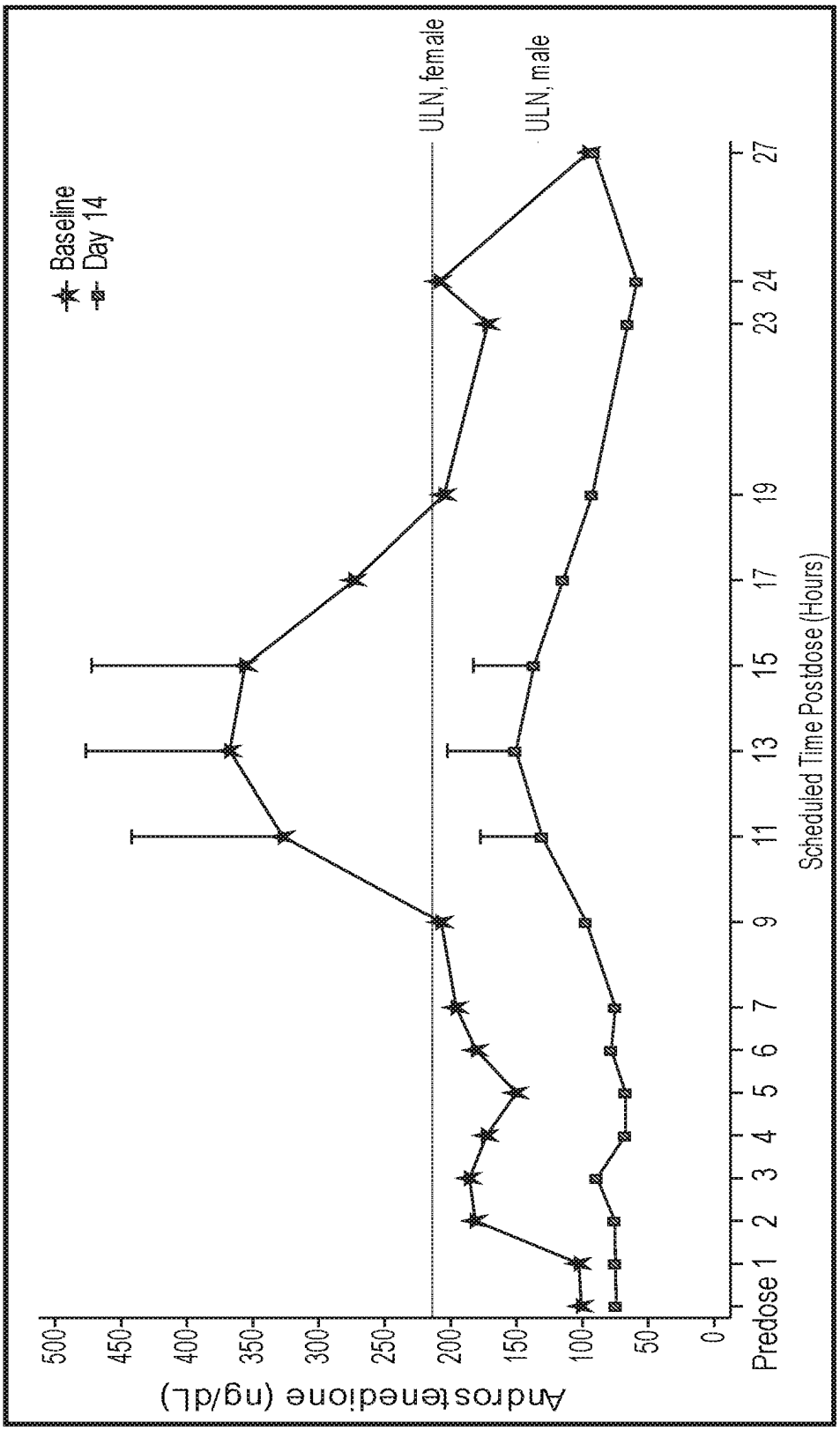

Baseline
Day 14
ULN, female
ULN, male
Androstenedione (ng/dL)
500
450
400
350
300
250
200
150
100
50
0
Predose 1 2 3 4 5 6 7 9 11 13 15 17 19 23 24 27
Scheduled Time Postdose (Hours)

FIG. 19C

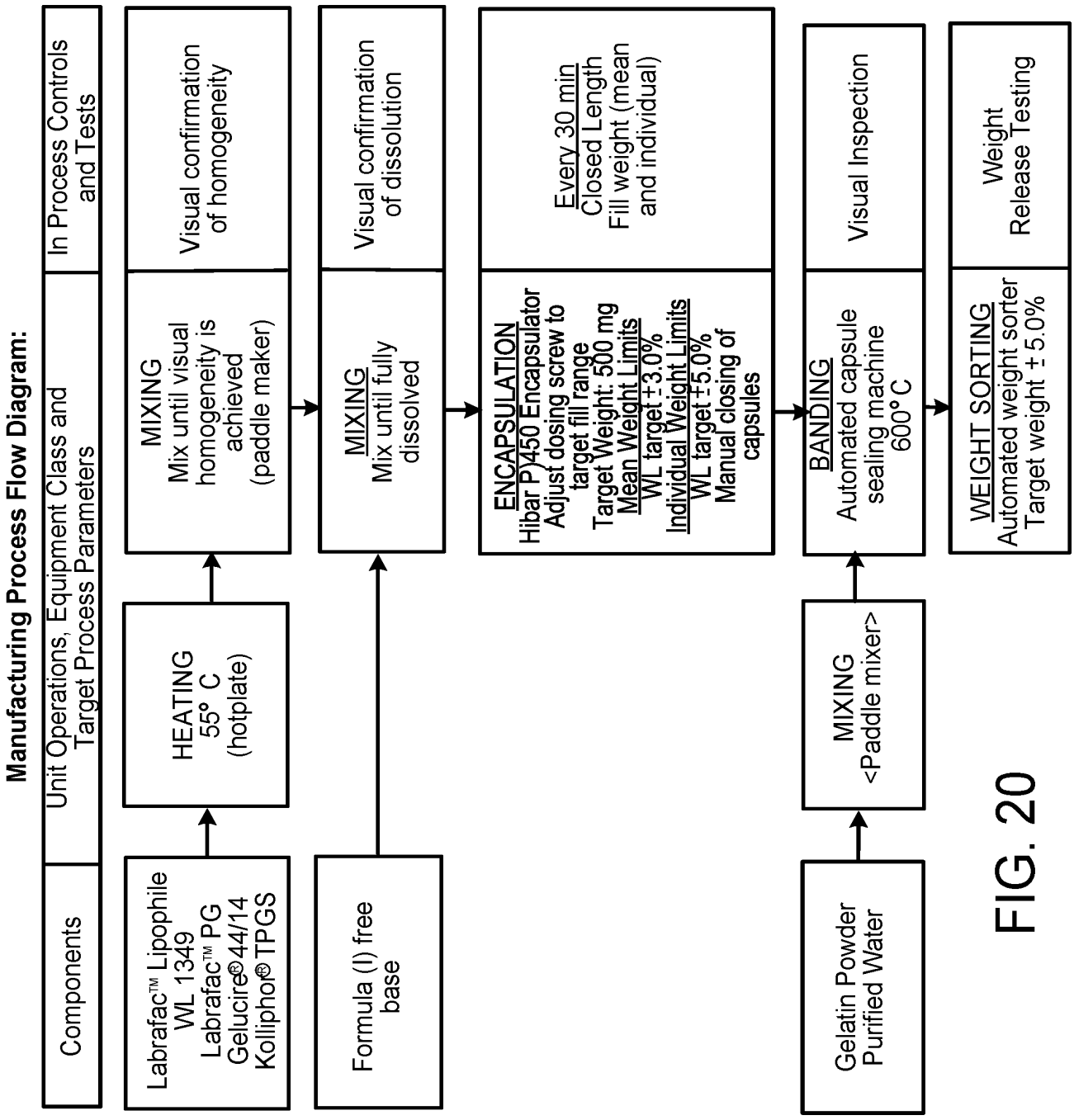
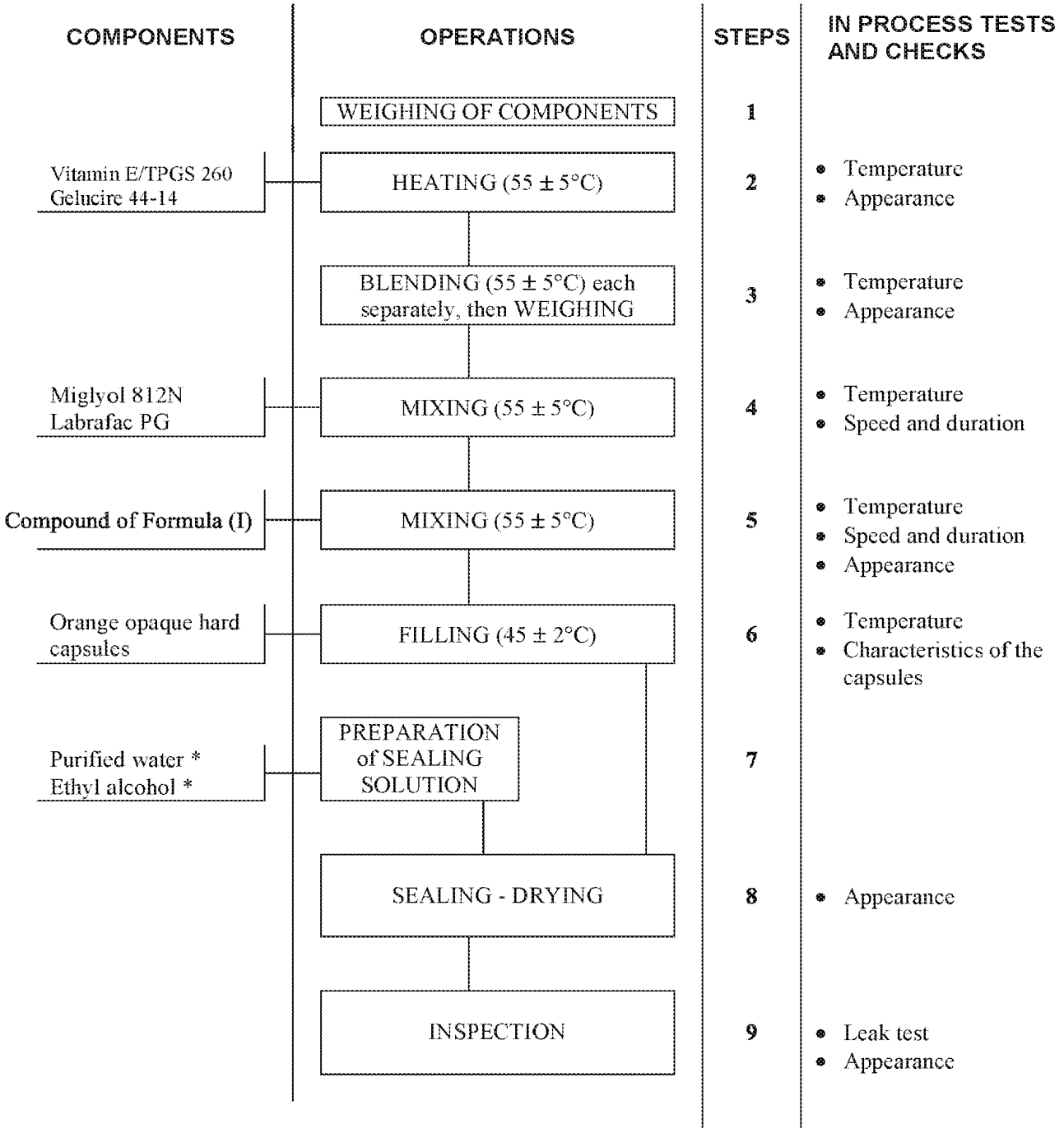

Manufacturing Process Flow Diagram:
Components
Unit Operations, Equipment Class and Target Process Parameters
In Process Controls and Tests
Labrafac™ Lipophile WL 1349
Labrafac™ PG
Gelucire®44/14
Kolliphor®TPGS
HEATING
55° C
(hotplate)
MIXING
Mix until visual homogeneity is achieved
(paddle maker)
Visual confirmation of homogeneity
Formula (I) free base
MIXING
Mix until fully dissolved
Visual confirmation of dissolution
ENCAPSULATION
Hibar PI/450 Encapsulator
Adjust dosing screw to target fill range
Target Weight: 500 mg
Mean Weight Limits
WL target ±3.0%
Individual Weight Limits
WL target ±5.0%
Manual closing of capsules
Every 30 min
Closed Length
Fill weight (mean and individual)
Gelatin Powder
Purified Water
MIXING
<Paddle mixer>
BANDING
Automated capsule sealing machine
600° C
Visual Inspection
WEIGHT SORTING
Automated weight sorter
Target weight ± 5.0%
Weight
Release Testing

FIG. 20



* Can be contained in hydro-alcoholic solution ready for manufacturing use

FIG. 21

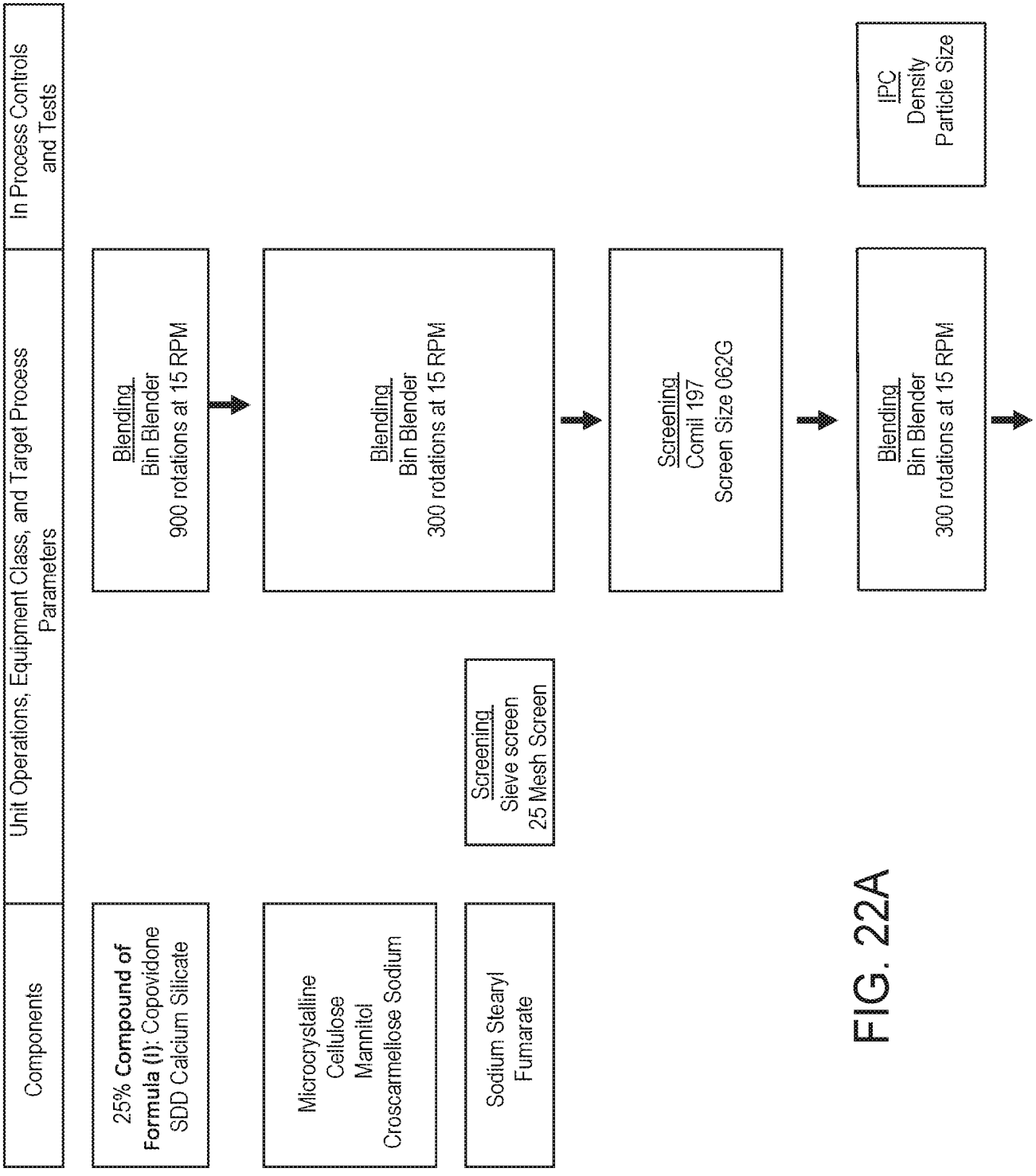

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
25% Compound of Formula (I): Copovidone SDD Calcium Silicate
Blending
Bin Blender
900 rotations at 15 RPM
Microcrystalline Cellulose Mannitol Croscarmellose Sodium
Blending
Bin Blender
300 rotations at 15 RPM
Sodium Stearyl Fumarate
Screening
Sieve screen
25 Mesh Screen
Screening
Comil 197
Screen Size 062G
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size

FIG. 22A

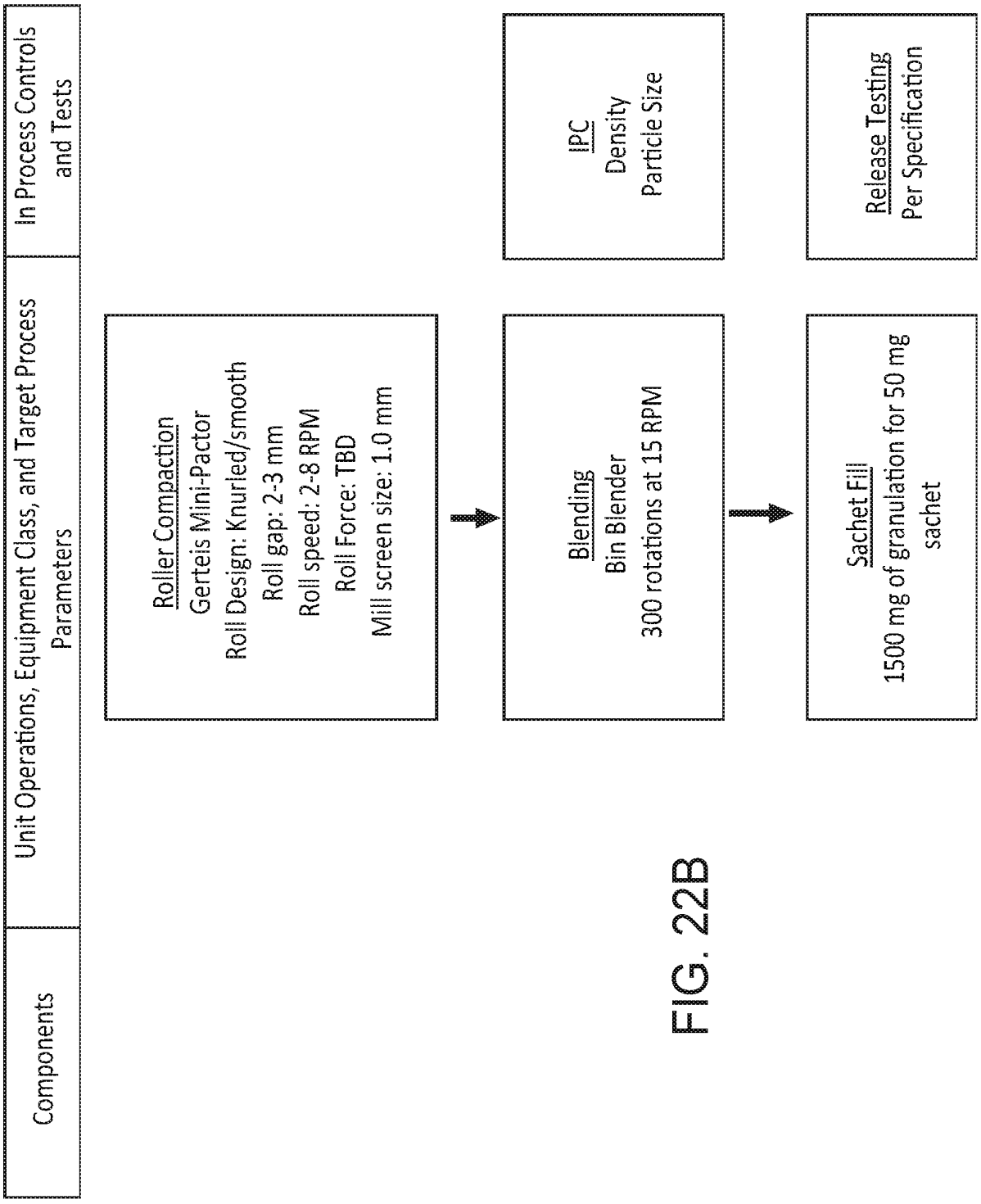

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
Roller Compaction
Gerteis Mini-Pactor
Roll Design: Knurled/smooth
Roll gap: 2-3 mm
Roll speed: 2-8 RPM
Roll Force: TBD
Mill screen size: 1.0 mm
Blending
Bin Blender
300 rotations at 15 RPM
IPC
Density
Particle Size
Sachet Fill
1500 mg of granulation for 50 mg sachet
Release Testing
Per Specification

FIG. 22B

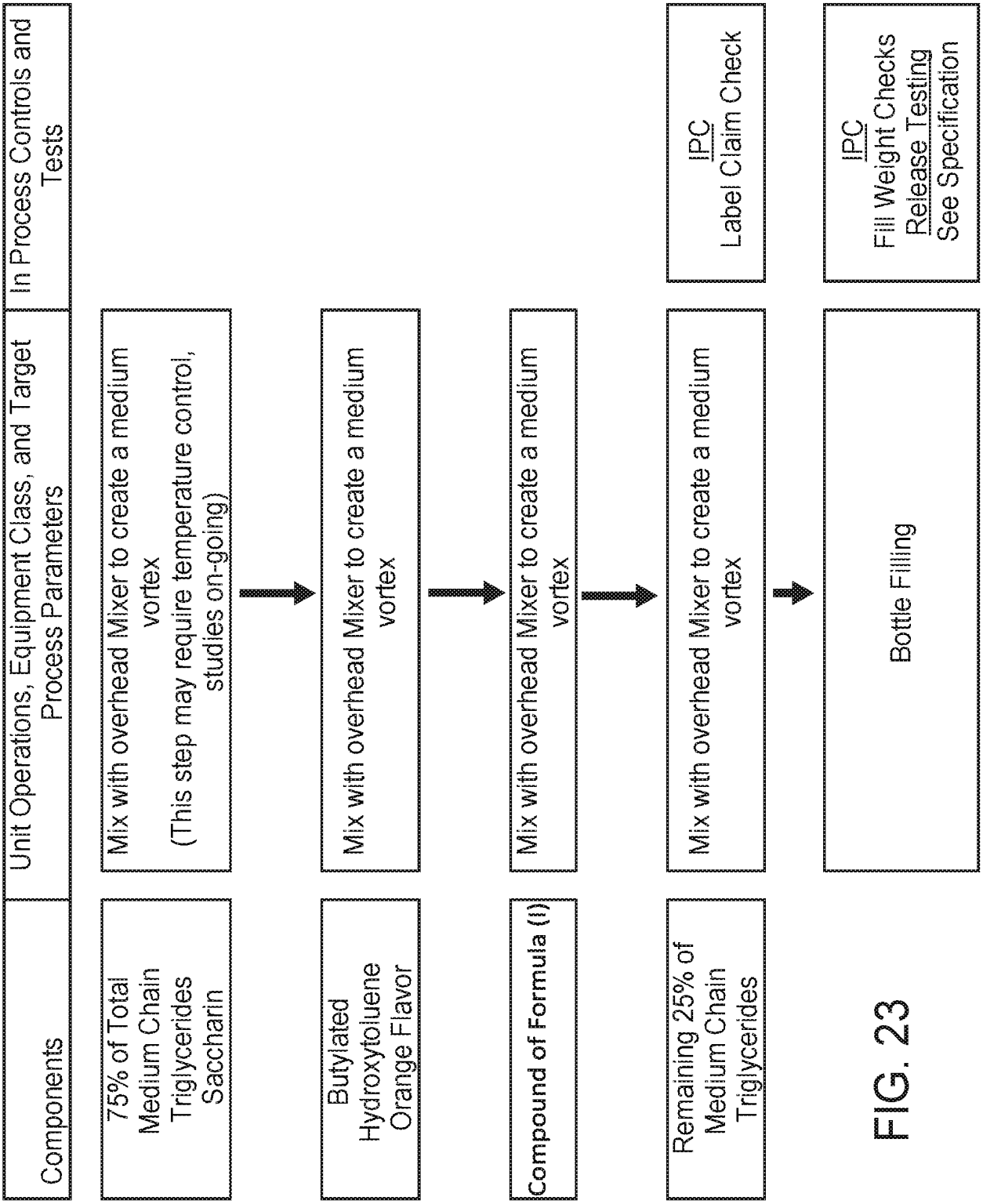

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides Saccharin
Mix with overhead Mixer to create a medium vortex
(This step may require temperature control, studies on-going)
Butylated Hydroxytoluene Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
IPC
Label Claim Check
Bottle Filling
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 23

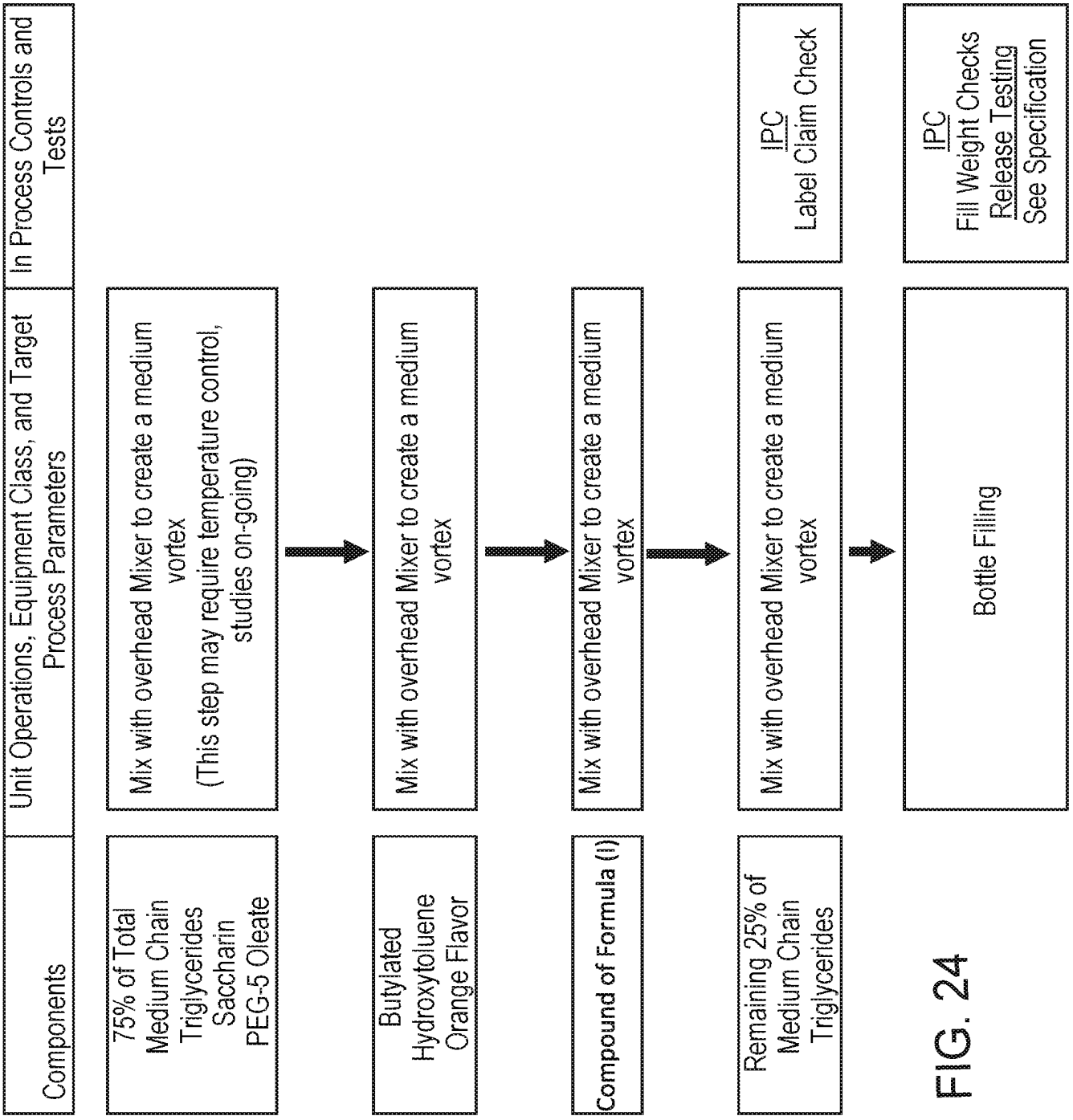

Components
Unit Operations, Equipment Class, and Target Process Parameters
In Process Controls and Tests
75% of Total Medium Chain Triglycerides
Saccharin
PEG-5 Oleate
Mix with overhead Mixer to create a medium vortex
(This step may require temperature control, studies on-going)
Butylated Hydroxytoluene
Orange Flavor
Mix with overhead Mixer to create a medium vortex
Compound of Formula (I)
Mix with overhead Mixer to create a medium vortex
Remaining 25% of Medium Chain Triglycerides
Mix with overhead Mixer to create a medium vortex
IPC
Label Claim Check
Bottle Filling
IPC
Fill Weight Checks
Release Testing
See Specification

FIG. 24

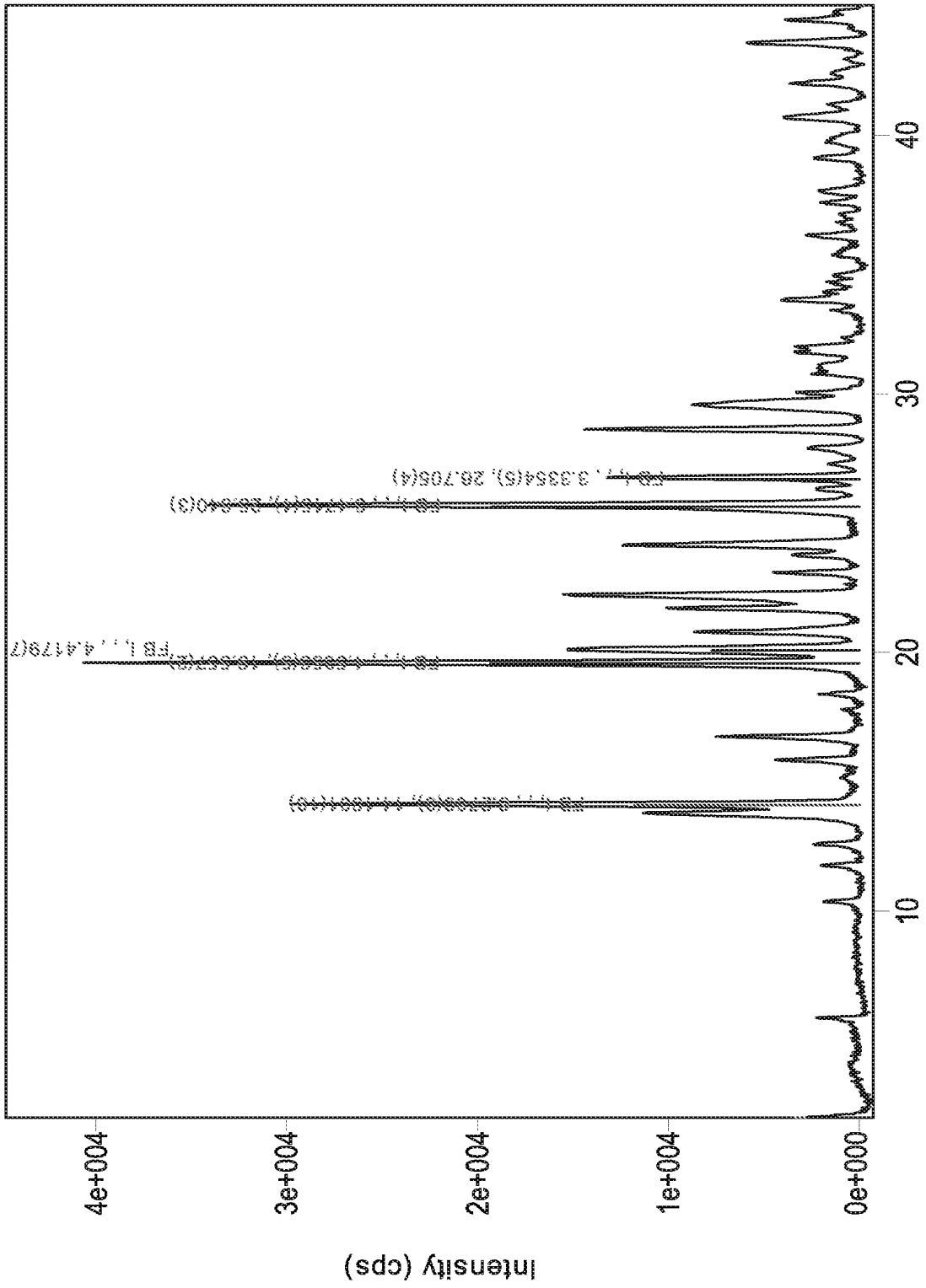

Intensity (cps)
4e+004
3e+004
2e+004
1e+004
0e+000
10
20
30
40
2-theta (deg)

FIG. 25

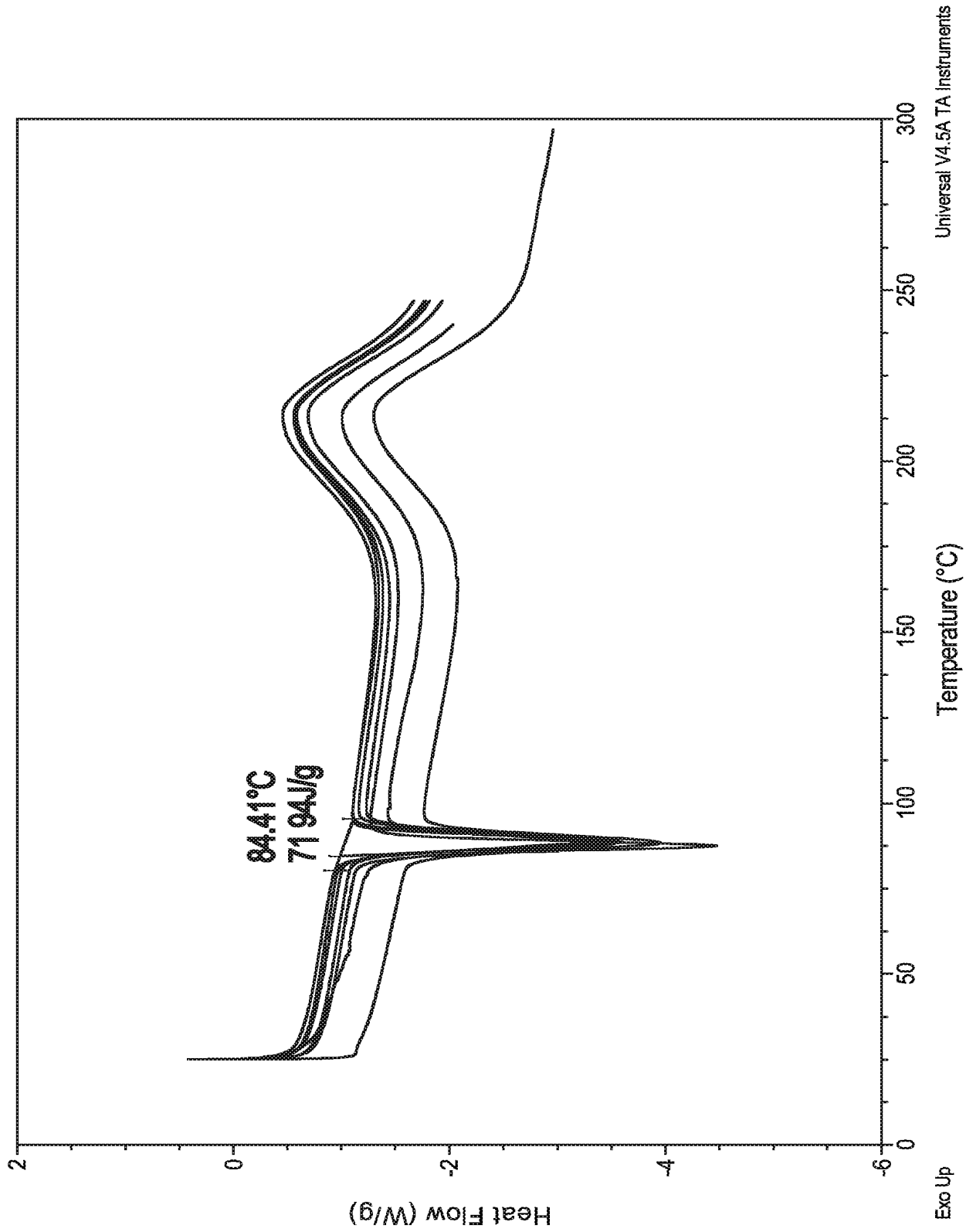

84.41°C
71.94J/g
Heat Flow (W/g)
Exo Up
Temperature (°C)
Universal V4.5A TA Instruments
2
0
-2
-4
-6
0
50
100
150
200
250
300

FIG. 26

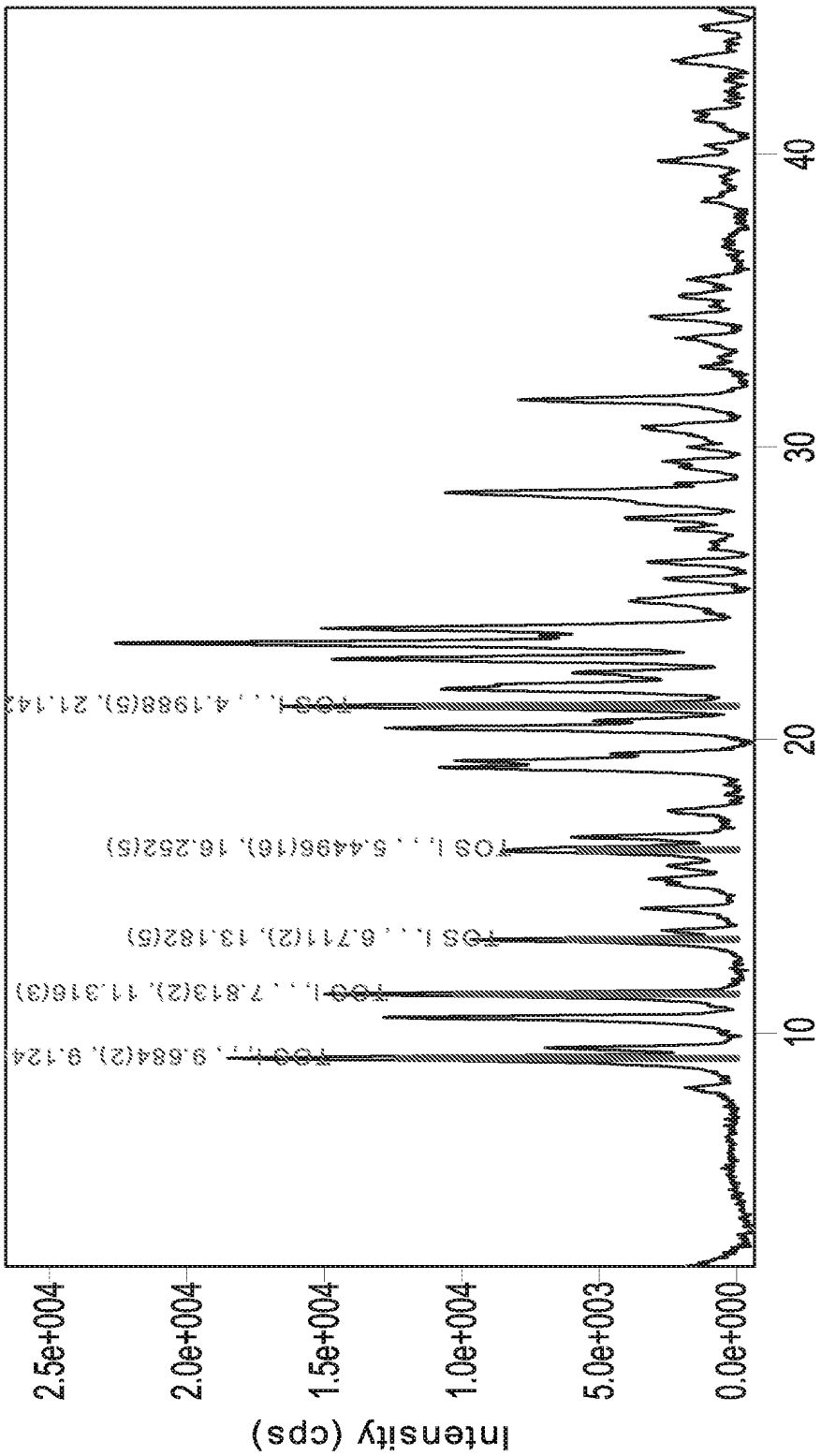

Intensity (cps)
2.5e+004
2.0e+004
1.5e+004
1.0e+004
5.0e+003
0.0e+000
10
20
30
40
2-theta (deg)

FIG. 27

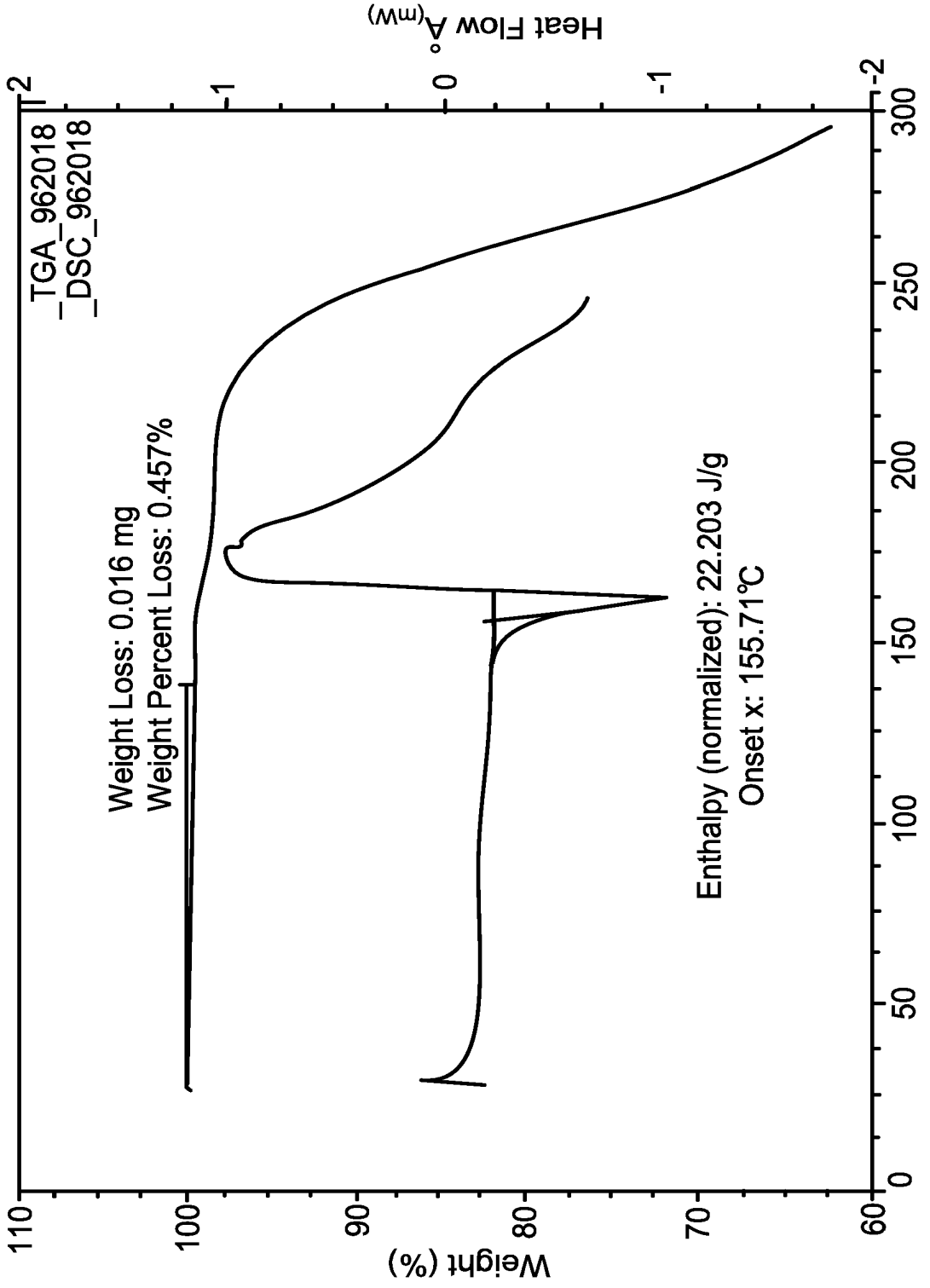

TGA_962018
DSC_962018
Weight Loss: 0.016 mg
Weight Percent Loss: 0.457%
Enthalpy (normalized): 22.203 J/g
Onset x: 155.71°C
Weight (%)
Heat Flow A (mW)
Temperature (°C)
110
100
90
80
70
60
2
1
0
-1
-2
0
50
100
150
200
250
300

FIG. 28

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/102194 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 25/20* (2006.01)
A61K 31/5025 (2006.01)

(21) International Application Number:
PCT/US2006/009942

(22) International Filing Date: 20 March 2006 (20.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/663,816 21 March 2005 (21.03.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

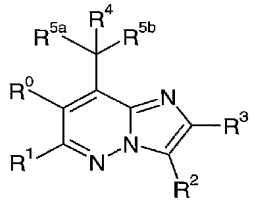
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOPYRIDAZINE COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel substituted imidazo[1,2-b]pyridazine compounds of Formula (I): pharmaceutical compositions thereof, and the use such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

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IMIDAZOPYRIDAZINE COMPOUNDS

Field of the Invention

This invention relates to novel substituted imidazo[1,2-b]pyridazine compounds, pharmaceutical compositions thereof, and the use of such compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists in the treatment of psychiatric disorders and neurological diseases.

Background of the Invention

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Natl. Acad. Sci* (*USA*) 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (1983); G. F. Koob, *Persp. Behav. Med.* 2:39 (1985); E. B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors [J. E. Blalock, *Physiological Reviews* 69:1 (1989); J. E. Morley, *Life Sci.* 41:527 (1987)].

There is evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souze, *Hosp. Practice* 23:59 (1988)]. Furthermore, CRF is known to have a broad extrahypothalmic distribution in the CNS, contributing therein to a wide spectrum of autonomic behavioral and physiological effects [see, e.g., Vale et al., 1983; Koob, 1985; and E. B. De Souze et al., 1985]. For example,

CRF concentrations are significantly increased in the cerebral spinal fluid of patients afflicted with affective disorder or major depression [C. B. Nemeroff et al., *Science* 226:1342 (1984); C. M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R. D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol. Psychiatry* 25:355 (1989)]. Moreover, excessive levels of CRF are known to produce anxiogenic effects in animal models [see, e.g., Britton et al., 1982; Berridge and Dunn, 1986 and 1987].

The density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C. B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (intravenously administered) observed in depressed patients [P.W. Gold et al., *Am. J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P. W. Gold et al., *New Engl. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R. M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of receptors in the brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF both in the conflict test [K. T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N. R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist Ro 15-1788, which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF [K. T. Britton et al., *Psychopharmacology* 94:396 (1988)]. Preliminary studies using the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrates that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C. W. Berridge and A. J. Dunn, *Horm. Behav.* 21:393 (1987), Brain Research Reviews 15:71 (1990)].

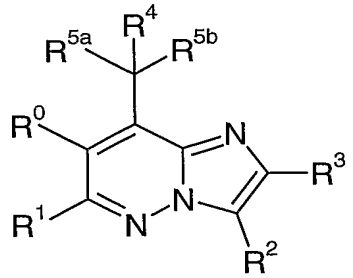
CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., *TIPS* 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., *Regul. Peptides* 71:15 (1997)]. For example, widely distributed brain CRF1 receptors are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., *Regul. Peptides* 59: 229-39 (1995); D. W. Schulz, *PNAS* 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs et al., 1997]. A more discrete septal/hypothalmic distribution [D. T. Chalmers et al., *J. Neurosci.* 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., *Nature* 378: 287-92 (1995)] suggest an altogether different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., *PNAS* 101(25): 9468-9473 (2004)]. In many cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion [S. C. Heinrichs, *Trends in Pharmacological Sciences* 20(8):311-5 (1999)]. While CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., *Neuroendocrinology* 80(2):111-23 (2004)].

In view of the above, efficacious and selective antagonists of CRF1 are desired as potentially valuable therapeutic agents for the treatment of psychiatric disorders and neurological diseases. It is thus desirable to discover new CRF1 antagonists.

SUMMARY OF THE INVENTION

The compounds of the present invention include CRF1 receptor antagonists.

One embodiment of the present invention is a compound of Formula I:



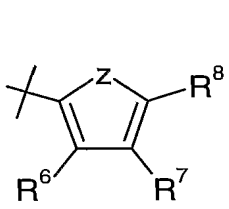
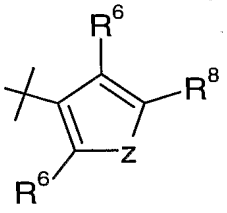
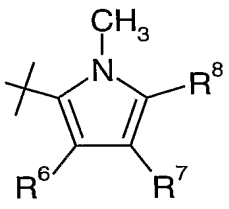
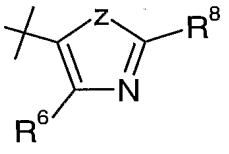
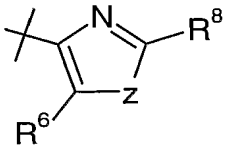
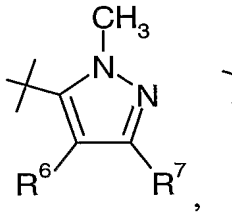
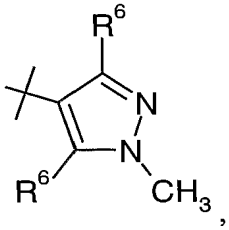
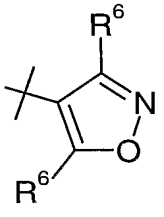
Formula I

wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

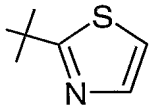
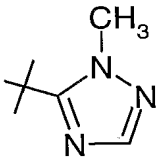
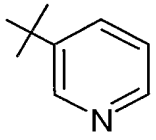
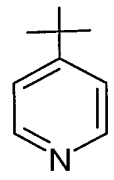
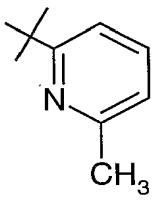
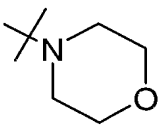
R^2 is selected from the group consisting of:


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,

,

,

, and

;

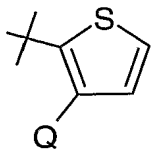
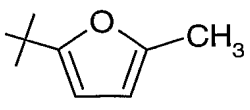
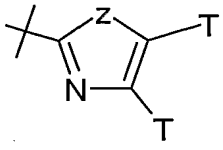
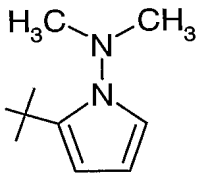
R^4 is hydrogen, halo, or hydroxy;

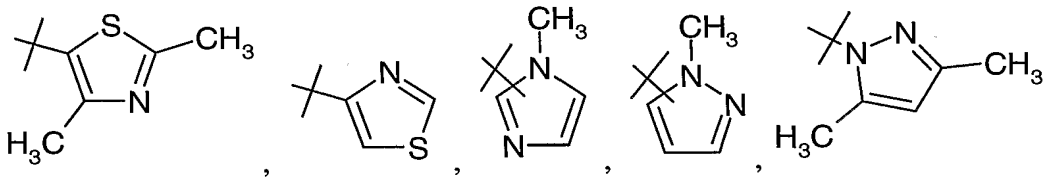
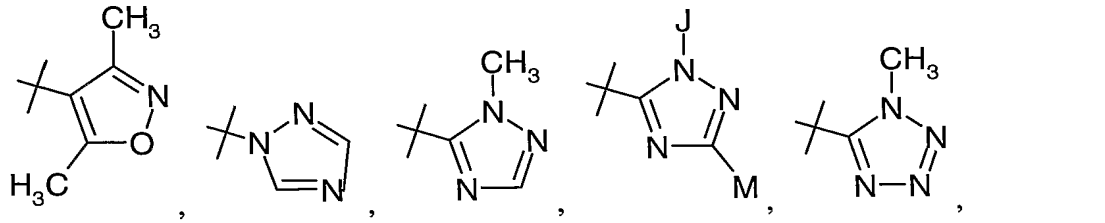
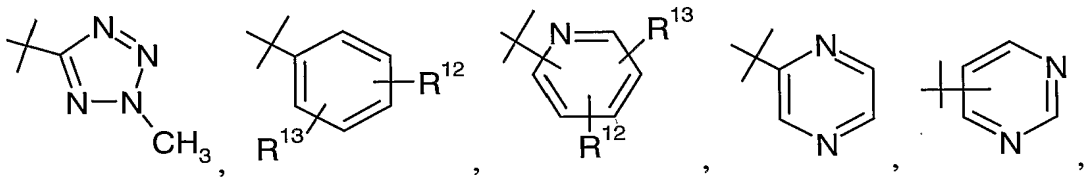
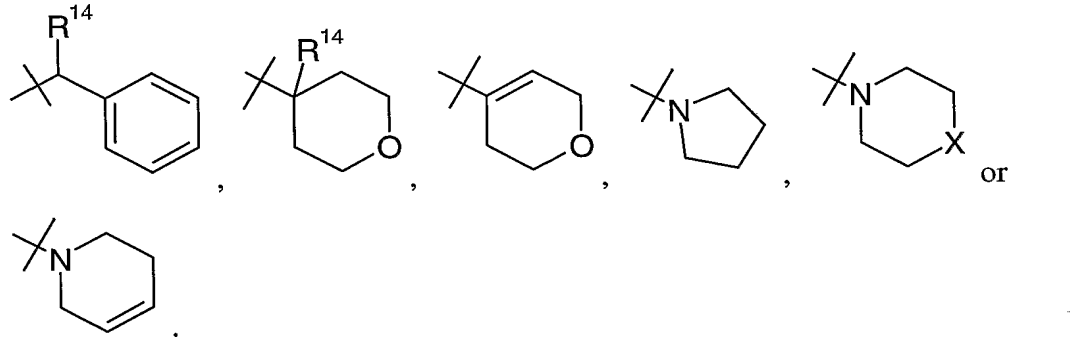
R^{5a} and R^{5b} are independently ethyl or n-propyl;

R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,

,

,

,

,

, or

;

R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,


,

,

,

,

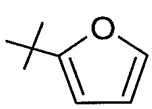
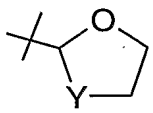
;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n\text{-}$, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is -CH_2- or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

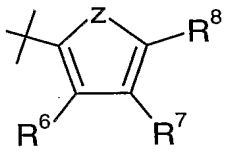
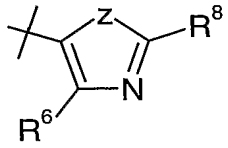
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

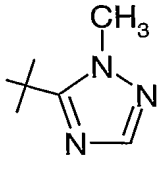
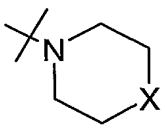
and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula I wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^2 is selected from the group consisting of  or  where z is S.

A further embodiment of the present invention is a compound of Formula I wherein R^7 is hydrogen.

Another another embodiment of the present invention is a compound of Formula I wherein R^6 is halo or methyl.

Yet another embodiment of the present invention is a compound of Formula I wherein R^8 is  or  where X is O.

Another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

Yet another embodiment of the present invention is a compound of Formula I, for use as a medicament.

A further embodiment of the present invention is use of a compound of Formula I for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal. In another further embodiment, the mammal is a human.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkoxy" means an alkyl-O- group, wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, and *n*-butoxy.

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

"Alkenyl" means an unsaturated aliphatic hydrocarbon group, which may be straight or branched, having 2 to 4 carbon atoms in the chain.

"Cycloalkyl" means a monocyclic group, having 3 to 5 carbon atoms.

"Halo" means fluoro, chloro, bromo, or iodo.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulphamates, malonates, salicylates, propionates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinateslaurylsulphonate salts, and the like. See, for example S.M. Berge, et al.,

"Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977). Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing. Company, Easton, Pa., 1985, p. 1418.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts thereof.

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The terms "treatment," "treat," "treating," and the like, are meant to include both slowing or reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

The symbol "——" in a molecular structure indicates the position of attachment for that particular substituent.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well- known principles of chemical structure connectivity.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

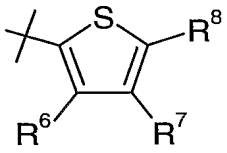
The present invention contemplates specific classes of compounds of Formula I. The following paragraphs describe such specific classes:

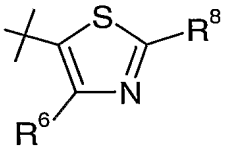
(a) R^0 is hydrogen;

(b) R^1 is methyl;

(c) R^3 is methyl;

(d) $R^1$and R^3 are methyl;

(e) R^2 is  ;

(f) R^2 is  ;

(g) R^4 is hydrogen;

(h) R^{5a} is ethyl;

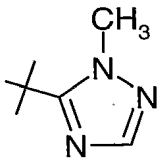
(i) R^{5b} is ethyl;

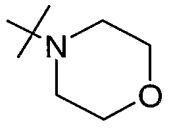
(j) R^{5a} and R^{5b} are ethyl;

(k) R^6 is halo;

(l) R^6 is methyl;

(m) R^7 is hydrogen;

(n) R^8 is  ;

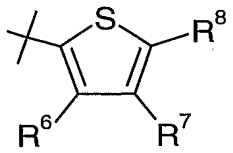
(o) R^8 is  .

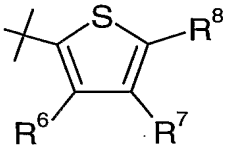
While all the compounds of Formula I are useful CRF1 receptor antagonists, the following paragraphs describe further specific classes:

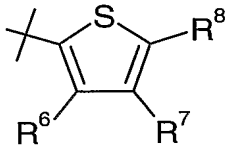
(a) Each of R^1 and R^3 is methyl and each of R^{5a} and R^{5b} is ethyl;

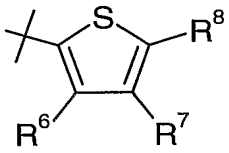
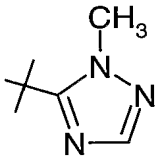
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 is hydrogen;

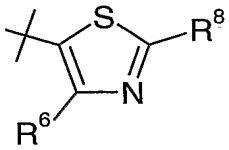
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen;

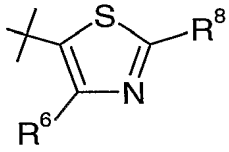
(d) R^2 is  and R^7 is hydrogen;

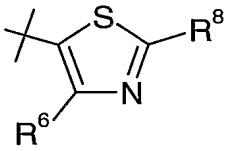
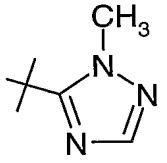
(e) R^2 is  , R^7 is hydrogen, and R^6 is halo;

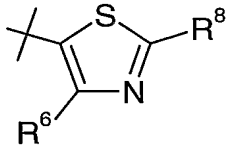
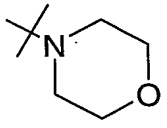
(f) R^2 is  , R^7 is hydrogen, and R^6 is methyl;

(g) R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

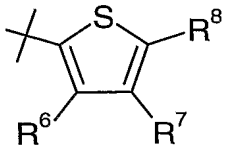
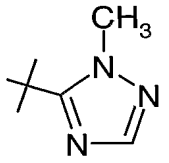
(h) R^2 is  and R^6 is halo;

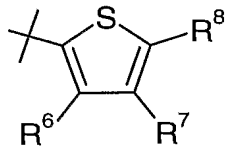
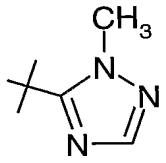
(i) R^2 is  and R^6 is methyl;

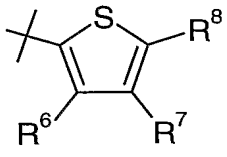
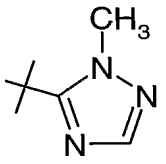
(j) R^2 is  , R^6 is halo or methyl, and R^8 is  ;

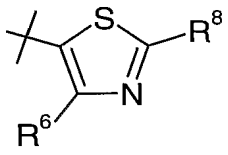
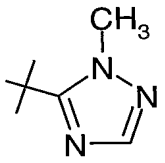
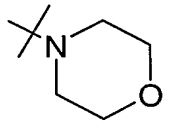
(k) R^2 is  , R^6 is halo or methyl, and R^8 is  .

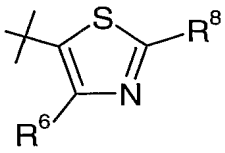
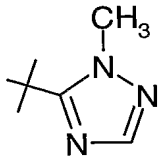
The following paragraphs describe even more specific classes of CRF1 receptor antagonists of the invention:

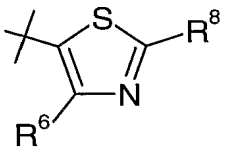
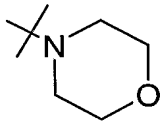
(a) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo or methyl, and R^8 is  ;

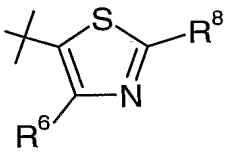
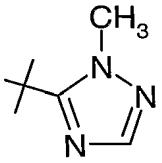
(b) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is halo, and R^8 is  ;

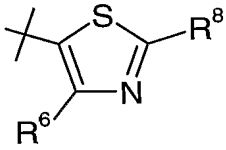
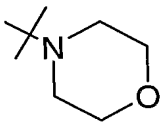
(c) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^7 is hydrogen, and R^6 is methyl, and R^8 is  ;

(d) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo or methyl, and R^8 is  or  ;

(e) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  ;

(f) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is halo, and R^8 is  .

(g) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  ;

(h) R^1 and R^3 are methyl, R^{5a} and R^{5b} are ethyl, and R^0 and R^4 are hydrogen, R^2 is  , R^6 is methyl, and R^8 is  .

Preferably compounds of the invention exhibit a Ki value for CRF1 binding of 1 micromolar or less, more preferably of 500 nanomolar or less. Even more preferably, compounds of the invention exhibit a Ki value for CRF1 binding of 250 nanomolar or less, with 100 nanomolar or less being even further preferred. With even greater preference, compounds of the invention exhibit a Ki value for CRF1 binding of 30 nanomolar or less, while 15 nanomolar or less is even more greatly preferred. Compounds of the invention exhibiting a Ki value for CRF1 binding of 5 nanomolar or less are most preferred.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient. A "pharmaceutically acceptable carrier, diluent, or excipient" is a medium generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers and excipients include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi- solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Descriptions of suitable

pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17 th ed., Mack Publishing Company, Easton, Pa., 1985.

These compounds of formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Dosage forms suitable for administration generally contain from about 1 mg to about 300 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of formula I are antagonists at the CRF1 receptor and are useful in the treatment of anxiety disorders, depression, major depressive disorder, and stress related disorders. Anxiety disorders are a group of diseases, recognized in the art, that includes phobic disorders, anxiety states, post-traumatic stress disorder and atypical anxiety disorders [The Merck Manual of Diagnosis and Therapy, 16 th edition (1992)]. Emotional stress is often a precipitating factor in anxiety disorders, and such disorders generally respond to medications that lower response to stress. The compounds are also useful in smoking cessation programs. The method of treatment involves administration to a mammal (e.g. a human) an effective amount of a compound of the invention. In particular, therapeutically effective amounts of the compounds of this invention are amounts effective to antagonize, or lower, levels of corticotropin releasing factor (CRF) in a mammal (e.g. a human), thereby alleviating in the mammal's conditions characterized by abnormally high levels of CRF expression.

As such, the present invention provides a method for treating a condition which is treatable by reducing CRF1 receptor stimulation, comprising administering to the mammal (e.g. a human) in need thereof a compound of Formula I, or a pharmaceutically acceptable salt thereof, in an amount effective to antagonize CRF1 receptor stimulation.

The present invention also provides use of a compound of Formula I for the manufacture of a medicament for treating a condition which is treatable by reducing CRF1 receptor stimulation.

The present invention also provides a method of antagonizing CRF1 receptors in a warm-blooded animal, comprising administering to the animal a compound of the invention at amount effective to antagonize CRF1 receptors. The warm-blooded animal is preferably a mammal, and more preferably a human.

The present invention also provides a method of treating a disorder in a warm-blooded animal, which disorder manifests hypersecretion of CRF, or the treatment of which disorder can be effected or facilitated by antagonizing CRF1 receptors, comprising administering to the animal a therapeutically effective amount of a compound of the invention. The warm-blooded animal is preferably a mammal, and more preferably a human.

Compounds of Formula I, or a pharmaceutically acceptable salt thereof, are useful for treating various disorders and conditions in a mammal (e.g. human) including social anxiety disorder; panic disorder; obsessive-compulsive disorder; major depressive disorder; anxiety with co-morbid depressive illness; affective disorder; anxiety; depression; irritable bowel syndrome; post-traumatic stress disorder; supranuclear palsy; immune suppression; gastrointestinal disease; anorexia nervosa, bulimia, or other feeding disorder; drug or alcohol withdrawal symptoms; substance abuse disorder (e.g., nicotine, cocaine, ethanol, opiates, or other drugs); inflammatory disorder; fertility problems; disorders the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF; a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; sleep disorders induced by stress; stress- related illnesses; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; chronic fatigue syndrome; stress- induced headache; headache; cancer; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, senile

dementia of the Alzheimer's type, and multiinfarct dementia; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; obesity and the metabolic syndrome; infertility; premature birth; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and heart related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, stress induced infections in humans and animals, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependences on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia.

A compound of this invention can be administered to treat the above disorders or abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal (e.g. human), such as by oral or parenteral administration using appropriate dosage forms. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The therapeutically effective amounts of the compounds of the invention for treating the diseases or disorders described above in a warm-blooded animal can be determined in a variety of ways known to those of ordinary skill in the art, e.g., by administering various amounts of a particular agent to an animal afflicted with a particular condition and then determining the effect on the animal. Typically,

therapeutically effective amounts of a compound of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect. It will be understood, however, that the specific dose levels for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease. Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most CNS disorders, a dosage regimen of four-times daily or less is preferred. For the treatment of stress and depression, a dosage regimen of one or two-times daily is particularly preferred.

It will be appreciated that all combinations of specific and preferred embodiments discussed above and the examples discussed below are contemplated as being encompassed by the present invention, provided such combinations do not comprise inconsistent groupings. In addition, all examples described herein are for illustrative purposes, and are not intended to narrow the scope of the invention in any way.

Compounds of the invention can generally be prepared using the synthetic routes illustrated in the Schemes below. Starting materials can be prepared by procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the schemes are as defined below or as in the claims.

The skilled artisan will appreciate that the introduction of certain substituents will create asymmetry in the compounds of Formula I. The present invention contemplates all enantiomers and mixtures of enantiomers and stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, including racemates. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral phase gas chromatography, chiral-phase high performance liquid chromatography, or crystallizing the compound as a chiral salt complex. Enantiomers and stereoisomers can

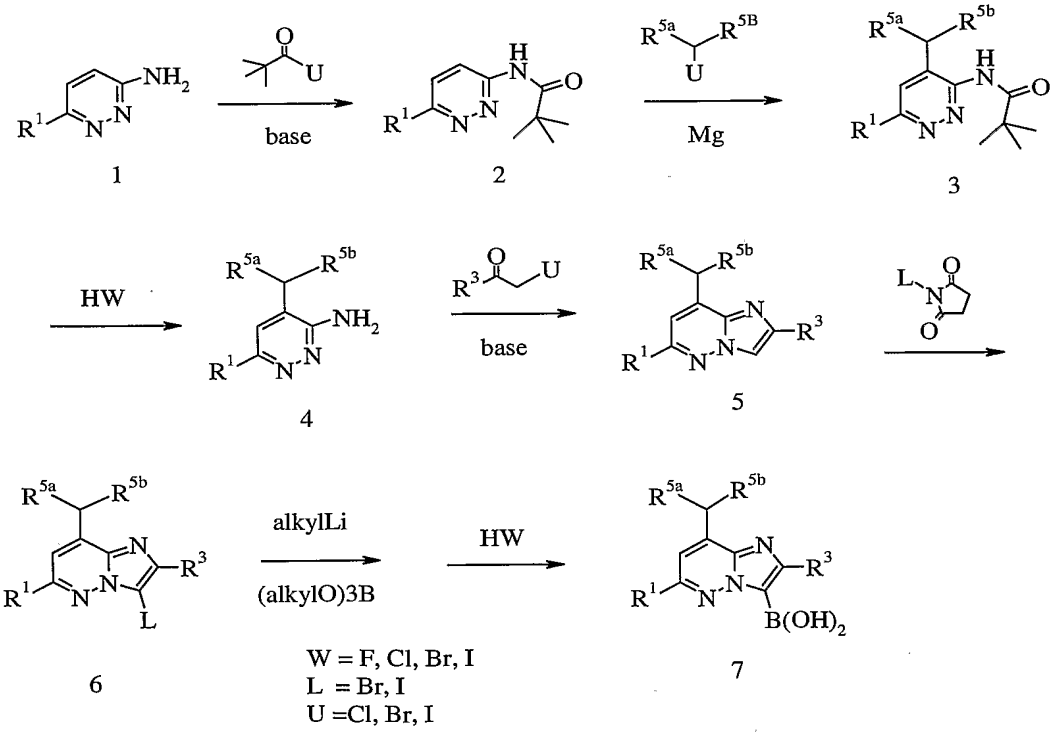
also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

Pharmaceutically acceptable salts are contemplated to be within the scope of the present invention. The compounds of the present invention are bases and salts of such compounds may be formed with acids, for example, a salt with inorganic acid such as hydrochloric acid or a salt with organic acid such as trifluoroacetic acid.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. These schemes, therefore, are not limited by the compounds listed nor by any particular substituents employed for illustrative purposes.

Scheme I

Synthesis of Imidazo[1,2-b]pyridazine fragment



R^1, R^3, R^{5a}, and R^{5b} are defined supra.

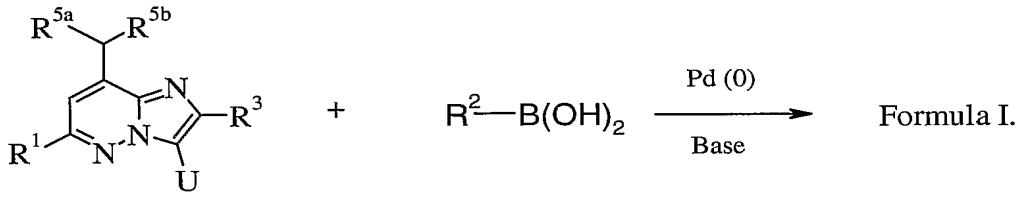
In Scheme I, a substituted 3-amino-pyridazine 1 is acylated with pivaloyl halide and a base, e.g., triethylamine in a polar aprotic solvent, e.g., methylene chloride at from

room temperature to the reflux to give amide 2. Amide 2 is treated with a Grignard reagent in diethylether or THF to give the 4-substituted amide 3. Amide 3 is hydrolyzed with aqueous HCl at from room temperature to 110 °C then neutralized to provide free amine 4. Amine 4 is treated with an alpha-halo ketone and base, e.g., sodium bicarbonate in 95% ethanol at from room temperature to 110 °C to give imidazopyridazine 5. Imidazopyridazine 5 is treated with a halogenating reagent e.g., N-iodo or N-bromosuccinimide in a polar aprotic solvent (e.g., acetonitrile) at from 0 °C to room temperature to give halide 6. Halide 6 undergoes halogen metal exchange with an alkyl lithium reagent, e.g., n-, sec-, or tert- butyllithium in diethylether or THF at from –78 °C to room temperature, followed by treatment with a trialkylborate, e.g., trimethylborate to give an intermediate boronic ester, which is hydrolyzed upon workup with aqueous HCl to provide boronic acid 7.

Scheme II

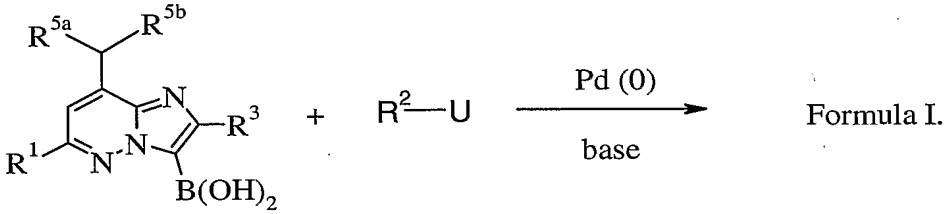
Synthesis of Compounds of Formula I by transition metal catalysis.

Equation 1.



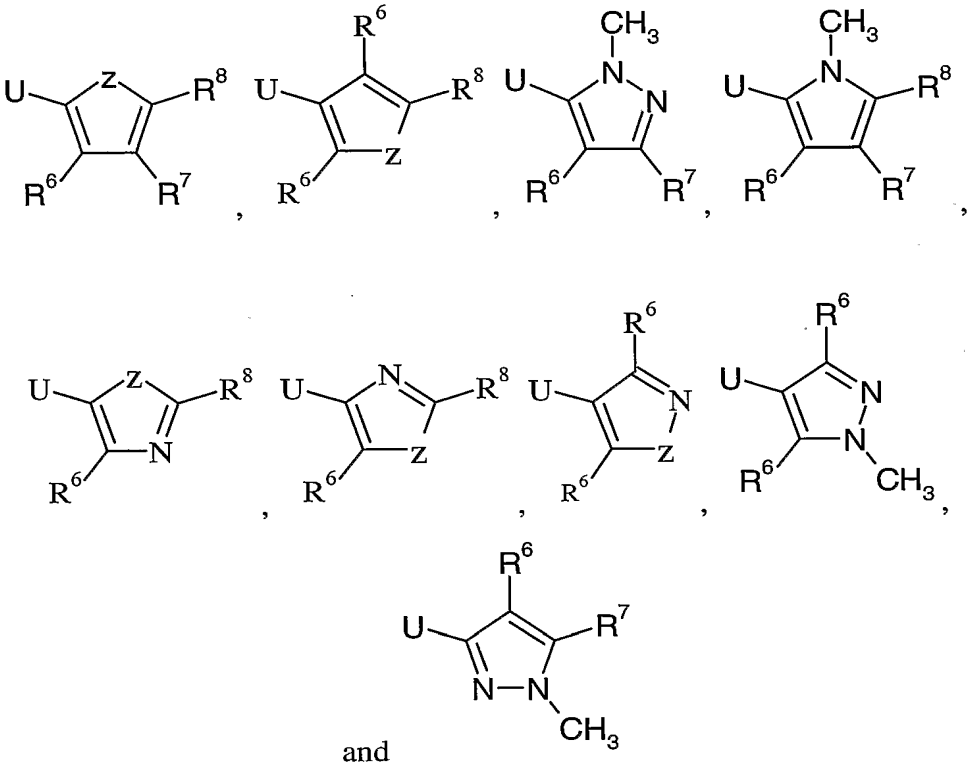
6 8

Equation 2.



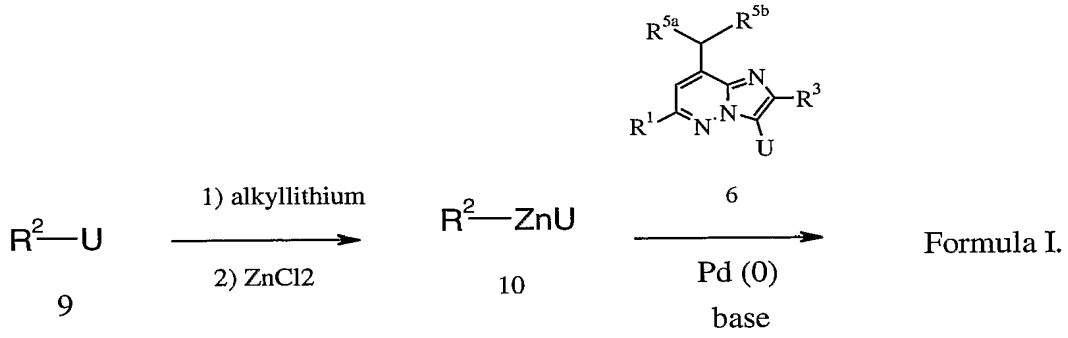
7 9

Where R^2-U is selected from the group consisting of:

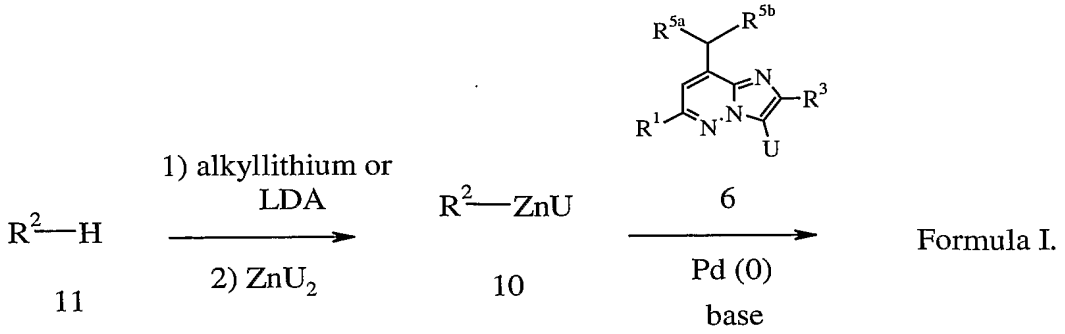


and

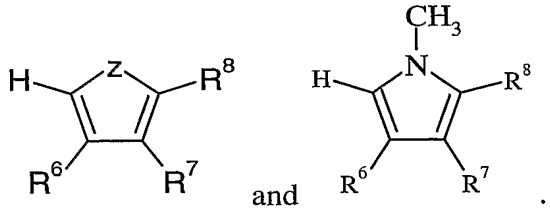
Equation 3.



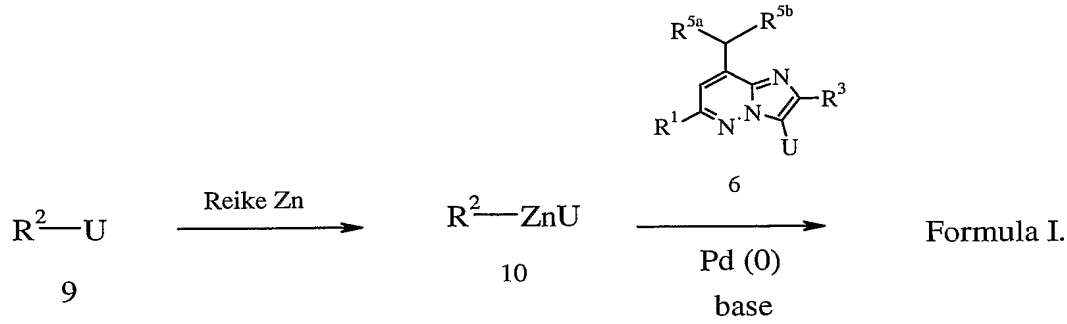
Equation 4.



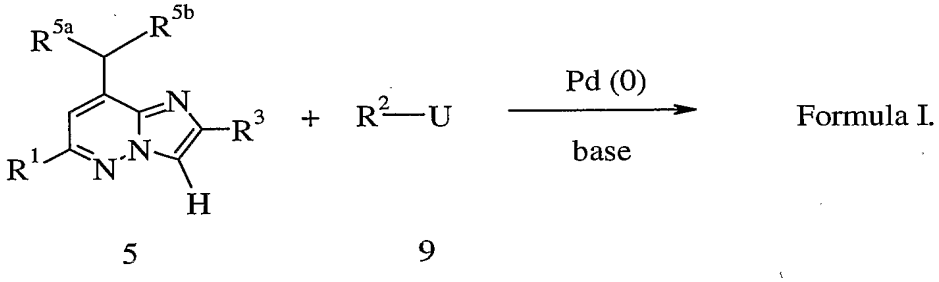
Where R^2-H is selected from the group consisting of:



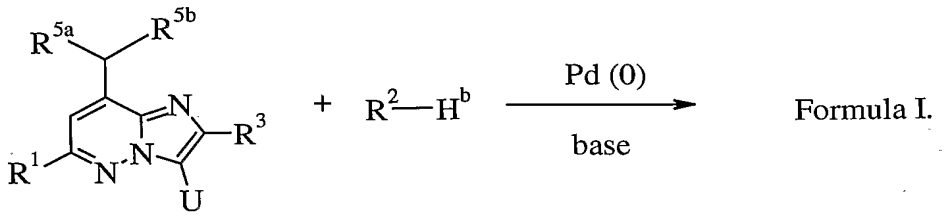
Equation 5.



Equation 6.

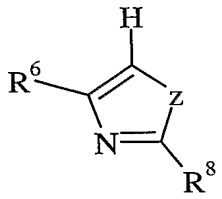


Equation 7.



6 12

Where R^2-H^b is selected from:



R^1, R^2, R^3, R^{5a}, R^{5b} R^6, R^7, R^8, U, and z are defined supra.

In Scheme II equation 1, halide 6 can be used in a coupling reaction with a 5-membered ring heterocyclic boronic acid 8 in the presence of palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give compounds of formula I.

Alternately in equation 2, boronic acid 7 can be used in a coupling reaction with a 5 membered ring heterocyclic halide 9 and palladium catalysis, e.g., tetrakis-triphenylphosphine palladium (0) in a lower alkanol (methanol or n- or i-propanol)/DME mixture at from 70-120 °C to give a compound of formula I.

In equation 3, 5-membered ring heterocyclic halides 9 may undergo halogen-lithium exchange with, e.g., n-, sec- or tert-butyl lithium in THF or ether at –65 °C, followed by lithium-zinc exchange with $ZnCl_2$ in either diethylether or THF at temperatures up to room temperature. The *in situ* organozinc reagent 10 may then undergo coupling with halide 6 in the presence of palladium, e.g., $PdCl_2$(dppf) in THF at from 70-120°C to give a compound of formula I.

In equation 4, a 5-membered heterocyclic ring with a ring proton may be lithiated by either an alkyllithium, e.g., n-, sec- or tert-butyl lithium or lithium diisopropyl amide in THF or ether at –65 °C to room temperature followed by lithium-zinc exchange with

anhydrous zinc halide in either diethylether or THF to give an organozinc reagent 10 that is used as in equation 3 above. One skilled in the art will also appreciate that commercially available organozinc reagents 10 can be used directly as an organozinc coupling partner.

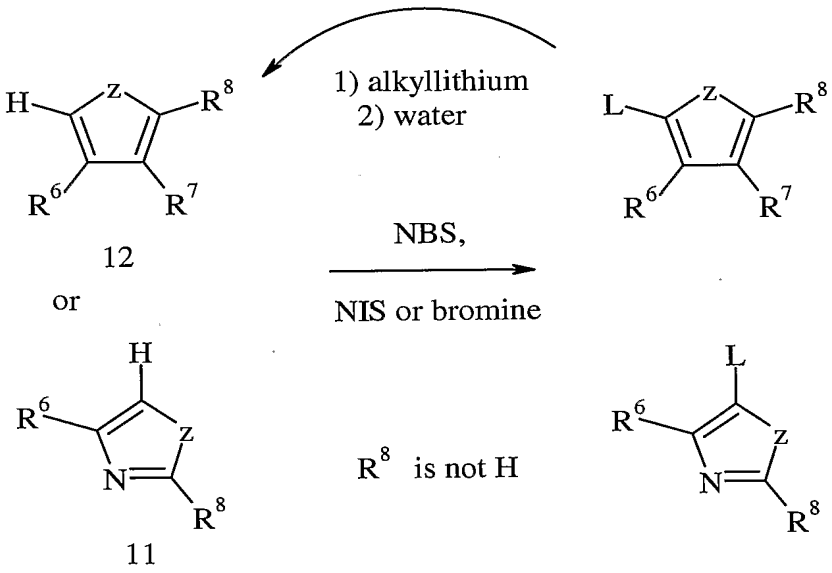
Furthermore from equation 5, it may be advantageous or convenient to use Reike Zn in THF to directly convert a 5-membered ring heterocyclic halide 9 to an organozinc reagent 10 for coupling with a halide 6.

In equation 6, a 5 membered heterocyclic halide 9 can be directly coupled with the imidazo[1,2-b]pyridazine intermediate 5 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$, Palladium acetate/TDBPP, or tetrakis-triphenylphosphine palladium (0) in DMF, THF, or NMP solvent from 70-120°C to give a compound of formula I.

Alternately, from equation 7, the imidazo[1,2-b]pyridazine halide 6 may be directly coupled with a 5 membered heterocycle 11 in the presence of palladium, e.g., $Pd_2(dba)_3$, $PdCl_2$ or Palladium acetate/TDBPP in DMF, THF, or NMP solvent from 70-120 °C to give a compound of formula I.

Scheme III

Synthesis of Substituted 5 Membered Heterocyclic Halides



R^6, R^7, R^8, L, and z are defined supra.

Several 5 membered heterocyclic rings and/or their bromides and/or iodides useful as starting materials for the synthesis of compounds of Formula I are commercially available or may be prepared by methods well know to the skilled artisan. From Scheme III, they may also be prepared by halogenation, e.g., with bromine, NBS or NIS. Furthermore, some of the intermediates 11 and 12 may be prepared by lithium halogen exchange followed by water quench.

Compounds of Formula I as intermediates in the preparation of other compounds of Formula I include the addition of aryllithium reagents (generated by the methods of equations 3 and 4 in Scheme II) to carbonyl compounds, e.g., aldehydes, ketones, esters, and Weinreb amides. The resulting carbinols or carbonyl compounds are further elaborated by halogenation under acidic conditions and by a second aryllithium addition, respectively.

Abbreviations

TBDMSCl or TBDMSiCl – tert-butyl-dimethylsilyl chloride

MS (ES) – Electrospray Mass spectrum

THF – tetrahydrofuran

DMSO – Dimethylsulfoxide

DMF – Dimethylformamide

DCM, CH2Cl2 – dichloromethane

Dioxane – 1,4-dioxane

N2 – nitrogen gas

NIS – N-iodosuccinimide

NBS – N-bromosuccinimide

MeOH - methanol

EtOH – 95% ethanol

RBF, RB – round bottom flask

RBSN – round bottom single neck flask

SiO2 – silica gel

EtOAc, AcOEt – ethylacetate

GFF - glass microfiber filter

HPLC – high pressure liquid chromatography on silica gel

ISCO – ISCO brand low pressure liquid chromatography on silica gel

AcCl – acetyl chloride

LDA – lithium diisopropylamine

KOAc – Potassium Acetate

TBABr – Tetrabutyl ammonium bromide

NMP – N-Methylpyrrolidinone

TDBPP – Tris (2,4-di-*t*-butylphenyl) phosphite.

Pd_2dba_3 – Tris(dibenzylideneacetone)dipalladium

$PdCl_2(dppf)$ – Dichloro(diphenylphosphinoferrocene)palladium

Tetrakis – tetrakis-(triphenylphosphine)-palladium

Dppf - 1,1'-bis(diphenylphosphino)ferrocene)

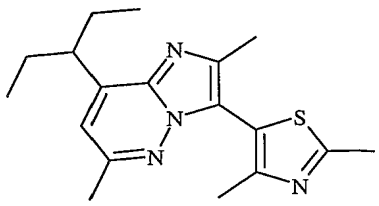
r.t., RT – room temperature

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following examples are provided to describe the invention in further detail. They are intended to illustrate and not to limit the invention in any way whatsoever. Examples 1-255 provide exemplary compounds and illustrate the preparation thereof. Examples A-D illustrate various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples.

Example 1.

Preparation of 8-(1-ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 6-Methyl-pyridizin-3-ylamine.

3-Chloro-6-methylpyridazine (25.0g, 0.229 moles) is dissolve in 250 mL of NH_4OH and heated to 170 °C in a sealed container for 24 hours. The solvents are evaporated. The residue is triturated in methylene chloride, and a solid is filtered. This trituration procedure is repeated with the filtrate four times. The filtered solids are combined and dried in a vacuum oven overnight to obtain the title compound as an off-white solid 4.32 g (0.040 moles, 20%). ^{1}H-NMR (dmso-d6): δ 7.1 (d, J = 8.9 Hz, 1H); 6.67 (d, J = 8.9 Hz, 1H); 6.04 (s, br, 2H); 2.33 (s, 3H) ppm. ES+ = 110 (100%, M + 1).

B. 2,2-Dimethyl-N-(6-methyl-pyridazine-3-yl)-propionamide.

Method 1: To a dry flask is added 7.12 g (0.065 mole) of 6-methyl-pyridizin-3-ylamine in 170 ml dry methylene chloride. Next, 14.5 ml of triethylamine is added and the reaction is cooled to 0 °C. Pivaloyl chloride (2.7 ml, 1.2 eq) is carefully added, and the reaction mixture is stir 10 minutes, removed from the bath, and stirred 4 hours more. Dichloromethane (200 mL) is added, and the reaction mixture is washed 3 times with saturated aqueous sodium bicarbonate, then brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to an oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient giving the title compound as a white solid weighing 1.51 g (7.8 mmoles, 42.7%). ^{1}H-NMR (DMSO-d_6), δ 10.39 (s, 1H); 8.11 (d, J = 9.30 Hz, 1H); 7.51 (d, J = 9.29 Hz, 1H); 2.54 (s, 3H); 1.23 (s, 9H) ppm. ES^+ = 194 (M+1).

Method 2: To a dry pressure tube is added 200 mg (1.56 mol) of 3-chloro-5-methylpyridazine, 190 mg (1.87 mmol) of trimethylacetamide, 14.6 mg (0.023 mmol) of rac-2,2'-bis(diphenylphosphine)-1,1'-binaphthyl , tris(dibenzylideneacetone)-dipalladium (0) , 762.4 mg (2.34 mmol) of cesium carbonate and 1.5 ml dry tetrahydrofuran. The pressure tube is purged with nitrogen and sealed. The reaction is heated to 100 °C overnight. The reaction is then cooled, diluted with dichloromethane, and filtered through celite. Solvents are evaporated and the crude product is purified via silica gel chromatography using a ethyl acetate:hexane gradient to obtain 91 mg (0.47 mmol, 30%) as a white solid.

C. N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Activated magnesium powder (19.2 g, 0.792 moles) is added to a dry 3 L flask fitted with a condensor and a drop funnel. The entire apparatus is heated with a gun dry under vacuum and allowed to cool. Enough ether is added to cover the magnesium. 3-Bromopentane (100 g, 0.662 mmol) is added to the addition funnel in 175 ml of diethyl ether. A 1/3 of the bromopentane solution is added to the magnesium and the reaction mixture is stirred under nitrogen until bubbling occurs. Then, the rest is dripped in at such a rate that the bubbling continues gently. The reaction is stirred for 30 minutes after bubbling ceases. Next, 2,2-dimethyl-*N*-(6-methyl-pyridazine-3-yl)-propionamide (21.3 g, 0.110 mmol) dissolved in 225 ml of dry THF is added dropwise. The reaction mixture is stirred for 1 hour. Saturated sodium tartrate (1 L) is carefully added, and the reaction is stirred for 30 minutes. The reaction mixture is transferred to a larger flask, 2 L of ethyl acetate is added, and the reaction is stirred 1 hour more. The layers are separate and the aqueous layer is extracted several times with ethyl acetate. The organic extracts are combined, and the solvents are evaporated. The residue is taken up in 600 mL of dichloromethane, and iodine (28 g, 0.110 mol) is added. The reaction is stirred for 2 hours. The organic layer is washed once with aqueous solution of sodium sulfite and then with water. The organic layer is dried over sodium sulfate, filtered, and evaporated to red oil. The crude product is purified via silica gel chromatography using a hexanes:ethyl acetate gradient. The product fractions are combined and evaporated. The residue is triturated in ethyl acetate and a light tan solid is filtered to obtain 12.0 g (45.6 mmol, 41 %) of the title compound. ^{1}H-NMR (DMSO-d_6), δ 9.88 (s, 1H); 7.59 (s, 1H); 2.60 (s, 3H); 2.39-2.42 (m, 1H); 1.21-1.37 (m, 2H); 1.38-1.43(m, 2H); 1.23(s, 9H); 0.71 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 264.

D. 4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine.

N-[4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-yl]-2,2-dimethyl-propionamide (12.0 g, 45 mmol) is dissolved in 60 mL of concentrated hydrochloric acid. The reaction mixture is heated to 95 °C in a sealed flask for 2 hours. The reaction is worked up by pouring over ice and extracting with ethyl acetate three times. The organic layer is discarded, and the pH of the aqueous layer is adjusted using 2 N sodium hydroxide. The basic solution is extracted with ethyl acetate five times. The organic extracts are

combined, dried over magnesium sulfate, filtered, and evaporated to obtain 6.68 g (37 mmol, 81%) of the title compound as a brownish oil. ^{1}H-NMR (DMSO-d_6), δ 6.95 (s, 1H); 5.89 (s, br, 2H); 2.52-2.56 (m, 1H); 2.34 (s, 3H); 1.44-1.58 (m, 4H); 0.72 (t, J = 7.04 Hz, 6H) ppm. MS/ES$^+$ = 180 (100%, M+1).

E. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

4-(1-Ethyl-propyl)-6-methyl-pyridazin-3-ylamine (850 mg, 4.74 mmol), chloroacetone (0.415 ml, 5.22 mL) and 20 mL of ethanol are heated in the microwave at 110 °C for 35 minutes. Sodium bicarbonate (1.2 g, 14.2 mmol) is added, and the reaction mixture is heated in an oil bath at 100 °C overnight. The solvent is evaporate and the residue is taken up in ethyl acetate and washed three times with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a brown oil. The crude product is purified via silica gel chromatography using a hexane:ethyl acetate gradient. The title compound is an oil weighing 3.69 g (17.0 mmol, 84%). ^{1}H-NMR (DMSO-d_6), δ 7.34 (s, 1H); 6.84 (s, 1H); 2.85-3.10 (m, 1H); 2.43 (s, 3H); 2.32 (s, 3H); 1.70-1.80 (m, 4H); 0.712 (t, J = 7.49 Hz, 6H) ppm. MS/ES$^+$ = 219 (100%, M+2).

F. 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.1 g, 0.023 moles) and 50 mL of dry acetonitrile are added to a nitrogen purged flask and are cooled to 0 °C. *NIS* (5.54 g,0.025 moles) in 90 mL of dry acetonitrile is added. The bath is allowed to come to room temperature, and the reaction to stir overnight. The solvents are evaporated. The residue is taken up in ethyl acetate, washed two times with 50% aqueous solution of sodium thiosulfate and with brine. The organic layer is dried over sodium sulfate, filtered, and evaporated to a residue again. The crude product is triturated in a small amount of acetonitrile, and a solid is filter off. The trituration is repeated several times to obtain the title compound as a light tan solid weighing 7.29 g (0.021 moles, 91%). ^{1}H-NMR (DMSO-d_6), δ 6.96 (s, 1H); 3.0-3.3 (m, 1H); 2.51 (s, 3H); 2.35 (s, 3H); 1.71-1.80 (m, 4H); 0.71 (t, J = 7.48 hz, 6H) ppm. MS/ES$^+$ = 344 (100%, M+1).

G. 8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid.

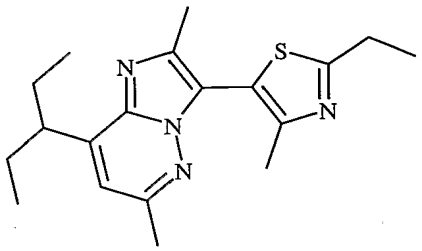
In an oven dried nitrogen purged 3 neck 50mL round bottom flask, 1.00g (2.91 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine in 60mL of dry THF is cooled to -78°C. 4.12mL (7.00mmol) of 1.7 M tert-butyllithium in hexanes is added and reaction is stirred at -78 °C for 1 hour. 0.818mL (7.30mmol) of trimethyl borate is added and reaction is followed by MS and TLC (1:1 Hexane:EA) Indication of product is observed by mass spectrum. The reaction is allowed to stir for an additional hour, quenched with 1 N hydrochloric acid, and diluted with ethyl acetate. The organic layer is separated, and the aqueous layer is extracted three times with 100 mL of ethyl acetate. The extracts are combined, dried over $MgSO_4$, filtered, and concentrated. The reaction residue is triturated in hexanes and a solid is filter off. MS, ES^+ = 262.2 (M+1).

H. 8-(1-Ethyl-propyl)-3-(2,4-dimethyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a microwave pressure tube is added 0.340g (1.30mmol) of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine-3-yl boronic acid, 0.100g (0.521mmol) of 5-bromo-2,4-dimethylthiazole, 0.361g (0.313mmol) of Pd(PPh3)4, 0.650mL (1.30mmol) of 2 M aqueous Na2CO3, and 2mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 40min. Reaction is checked by MS which indicates product present. The reaction mixture is partitioned between 75mL of ethyl acetate and 75mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.100g of the product, 58% yield. MS, ES+ = 329.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.974 (s, 1H); 3.085-3.052 (m, 1H); 2.665 (s, 3H); 2.438 (s, 3H); 2.290 (s, 3H); 2.147 (s, 3H); 1.849-1.727 (m, 4H); 0.776-0.738 (m, 6H) ppm.

Example 2.

Preparation of 8-(1-ethyl-propyl)-3-(2-ethyl-4-methyl-5- yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-ethyl-4-methylthiazole.

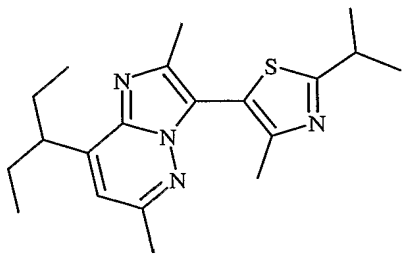
In an oven dried, N_2 purged, 50 mL round bottom flask, 1.00 g (7.86 mmol) of 2-ethyl-4-methylthiazole is reacted with 0.487 mL (9.43 mmol) of bromine in 7mL of acetic acid at room temperature. Reaction is checked by MS after 2 hours. The reaction mixture is partitioned between 50 mL H_2O and 25 mL of CH_2Cl_2. The layers are separated and the aqueous is extracted 3X25mL of CH_2Cl_2. The organics are combined and washed 1X25mL 1N $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated under vacuum to give 1.38g of the title compound, 85% yield. MS, ES+ = 206.0 (M+1); ^{1}H-NMR (DMSO-d6) = 2.940-2.810 (m, 2H); 2.253-2.251 (m, 3H); 1.225-1.222 (m, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-ethyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-ethyl-4-methylthiazole produces the title product in 27% yield. MS, ES+ = 343.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.975 (s, 1H); 3.090-3.056 (m, 1H); 3.025-2.968 (m, 2H); 2.439 (s, 3H); 2.291 (s, 3H); 2.155 (s, 3H); 1.835-1.744 (m, 4H); 1.338-1.300 (m, 3H); 0.776-0.740 (m, 6H) ppm.

Example 3.

Preparation of 8-(1-ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-2-isopropyl-4-methylthiazole.

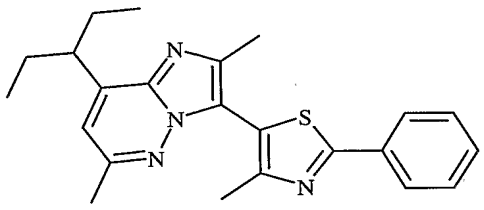
Using a procedure similar to Example 2A, 2-isopropyl-4-methylthiazole produces the title product in 90% yield. MS, ES+ = 220.0 (M+1); ^{1}H-NMR (DMSO-d6) = 3.210-3.175 (m, 1H); 2.257 (s, 3H); 1.264-1.248 (d, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(2-isopropyl-4-methyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-2-isopropyl-4-methylthiazole produces the title product in 29% yield. MS, ES+ = 357.2 (M+1); ^{1}H-NMR (DMSO-d6) = 6.990 (s, 1H); 3.120-3.050 (m, 1H); 2.442 (s, 3H); 2.294 (s, 3H); 2.158 (s, 3H); 1.810-1.750 (m, 4H); 1.362-1.344 (d, 6H); 0.777-0.741 (m, 6H) ppm.

Example 4.

Preparation of 8-(1-ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-phenylthiazole.

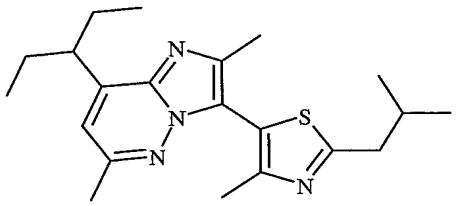
Using a procedure similar to Example 2A, 4-methyl-2-phenylthiazole produces the title product in 90% yield. MS, ES+ = 256.0 (M+1); ^{1}H-NMR (DMSO-d6) = 7.900-7.867 (m, 2H); 7.538-7.512 (m, 3H); 2.407 (s, 3H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-phenyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-phenylthiazole produces the title product in 24% yield. MS, ES+ = 391.3 (M+1); ^{1}H-NMR (DMSO-d6) = 8.005-7.995 (m, 2H); 7.538-7.534 (m, 3H); 7.010 (s, 1H); 3.185-3.095 (m, 1H); 2.496 (s, 3H); 2.394 (s, 3H); 2.316 (s, 3H); 1.895-1.785 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 5.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-methyl)propyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-4-methy-2-(2-methyl)propylthiazole.

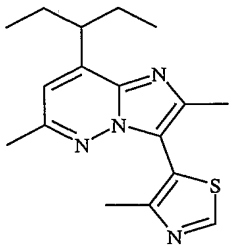
Using a procedure similar to Example 2A, 4-methyl-2-(2-methyl)propylthiazole produces the title product in 96% yield. MS, ES+ = 234.1 (M+1); ^{1}H-NMR (DMSO-d6) = 2.744 (m, 2H); 2.259 (s, 3H); 1.895-2.000 (m, 1H); 0.905-0.888 (m, 6H) ppm.

B. 8-(1-Ethyl-propyl)-3-(4-methyl-2-(2-methyl)propyl-5-thiazolyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 1H, 5-bromo-4-methyl-2-(2-methyl)propylthiazole produces the title product in 7% yield. MS, ES+ = 371.3 (M+1); ^{1}H-NMR (DMSO-d6) = 7.013 (s, 1H); 3.109 (m, 1H); 2.892-2.875 (d, 2H); 2.517 (s, 3H); 2.513 (s, 3H); 2.476 (s, 3H); 2.107-2.073 (m, 1H); 1.868-1.780 (m, 4H); 1.018-1.002 (d, 6H); 0.813-0.775 (m, 6H) ppm.

Example 6.

Preparation of 8-(1-Ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

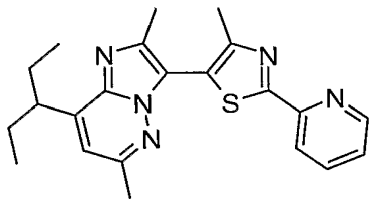


3.00 g of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (8.74 mmol), 4.32 g of 4-methyl-2*H*-thiazole (43.6 mmol), 453 mg of triphenylphosphine (1.73 mmol) and 5.85 g of cesium carbonate (18.0 mmol) are placed into the sealed tube with

20 ml of DMF and N2 gas is bubbled in for 40 min. 39 mg of Pd2dba3 (0.43 mmol) is added and the tube is sealed and heated at 130°C overnight. The cooled reaction mixture is filtered and applied onto silica-gel column (Hexane → Hexane : AcOEt = 3: 1) to give 2.12 g of the title compound (77%).^{1}H-NMR (DMSO-d6) δ 9.215 (s, 1H); 6.993 (s, 1H); 3.079 (m, 1H); 2.480 (s, 3H); 2.439 (s, 3H); 2.302 (s, 3H); 1.824-1.751 (m, 4H); 0.780-0.743 (m, 6H) ppm. MS, ES+ = 315.2.

Example 7.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.



A. 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

In an oven dried, N2 purged, 15mL round bottom flask, 0.028 g (0.089 mmol) of 8-(1-ethyl-propyl)-3-[4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. in 1.5mL of dry CH_2Cl_2 is cooled to 0 C. 0.019 g (0.107 mmol) of NBS is added and reaction is stirred overnight allowing bath to come to room temperature. Reaction mixture is directly purified by chromatography using hexane/ethyl acetate as solvent system. The product containing fractions are combined to obtain 0.012 g, 34% yield. MS, ES+ = 395.1 (M+1); ^{1}H-NMR (DMSO-d6) = 7.070 (s, 1H); 3.10 (m, 1H); 2.49 (s, 3H); 2.36 (s, 3H); 2.25 (s, 3H); 1.85-1.78 (m, 4H); 0.81-0.77 (m, 6H) ppm.

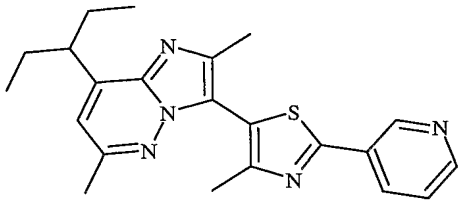
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-2-yl-thiazol-5-yl)-imidazo[1,2-*b*]pyridazine.

A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine (380 mg, 0.96 mmol), 2-pyridinezinc bromide (0.5 M in THF, 2.1 mL, 4 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and THF (3 mL) is heated at 80 °C for 18 hours. Ethyl acetate (20 mL) is added. The organic layer is separated, dried over

magnesium sulfate, filtered, and the solvent removed in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate as eluent to produce the title compound 325 mg (86%). ^{1}H-NMR ($CDCl_3$), δ 9.55 (m,1H); 8.10 (m, 1H); 7.73 (m,1H); 7.26 (m,1H); 6.58 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 8.

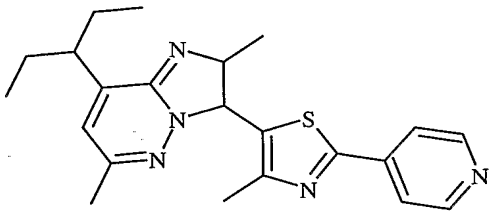
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.070 g (0.178 mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.066g (0.534 mmol) of pyridine-3-boronic acid, 0.103 g (0.089 mmol) of Pd(PPh3)4, 0.267mL (0.534 mmol) of 2 M aqueous Na2CO3, and 1mL 7:3:2 DME:H2O:EtOH, and the mixture is heated at 160 °C for 60 min. The reaction mixture is partitioned between 25mL of ethyl acetate and 25 mL of water. The layers are separated and the aqueous is extracted 3X 25 mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using hexanes/Ethyl acetate as a solvent system. The product containing fractions are combined to obtain 0.045 g of the product, 64% yield. MS, ES+ = 392.2 (M+1); ^{1}HNMR (DMSO-d6) δ 9.18 (s, 1H); 8.65 (m, 1H); 8.34 (d, 1H); 7.60 (m, 1H); 7.06 (s, 1H); 3.06 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.34 (s, 3H); 1.87-1.82 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 9.

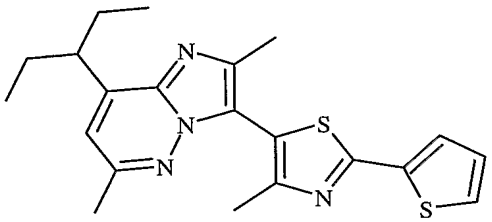
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-pyridyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, pyridine-4-boronic acid produces the title compound in 10% yield. MS, ES+ = 392.3 (M+1); ^{1}HNMR (DMSO-d6) = 8.79 (s, 2H); 7.80 (m, 2H); 7.07 (s, 1H); 3.12 (m, 1H); 2.50 (s, 3H); 2.40 (s, 3H); 2.36 (s, 3H); 1.90-1.80 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 10.

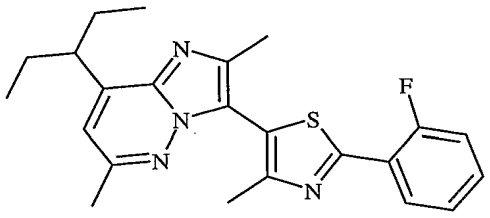
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(thiophene-2-yl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, thiophene-2-boronic acid produces the title compound in 89% yield. MS, ES+ = 397.1 (M+1); ^{1} H-NMR (DMSO-d6) = 7.81-7.79 (d, 1H); 7.78-7.77 (d, 1H); 7.21-7.20 (m, 1H); 7.05 (s, 1H); 3.19-3.15 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.27 (s, 3H); 1.85-1.83 (m, 4H); 0.82-0.79 (m, 6H) ppm.

Example 11.

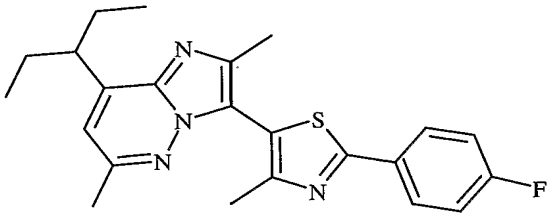
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2-fluorophenyl boronic acid produces the title compound in 82% yield. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.32-8.28 (m, 1H); 7.60-7.58 (m, 1H); 7.57-7.41 (m, 2H); 7.05 (s, 1H); 3.13-3.12 (m, 1H); 2.49 (s, 3H); 2.40 (s, 3H); 2.35 (s, 3H); 1.91-1.780 (m, 4H); 0.87-0.79 (m, 6H) ppm.

Example 12.

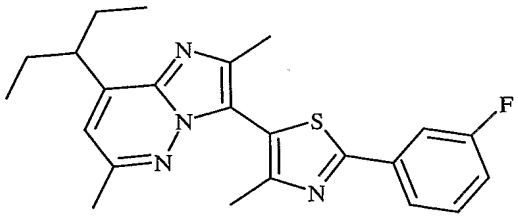
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluorophenyl boronic acid produces the title compound in 63% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.06-8.03 (m, 2H); 7.408-7.36 (m, 2H); 7.05 (s, 1H); 3.14-3.11 (m, 1H); 2.50 (s, 3H); 2.39 (s, 3H); 2.31 (s, 3H); 1.90-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 13.

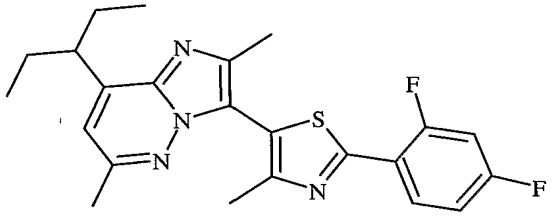
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3-fluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3-fluorophenyl boronic acid produces the title compound in 77% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 409.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.84-7.78 (m, 2H); 7.64-7.57 (m, 2H); 7.41-7.36 (m, 1H); 7.06 (s, 1H); 3.15-3.111 (m, 1H); 2.45 (s, 3H); 2.40(s, 3H); 2.32 (s, 3H); 1.91-1.78 (m, 4H); 0.83-0.79 (m, 6H) ppm.

Example 14

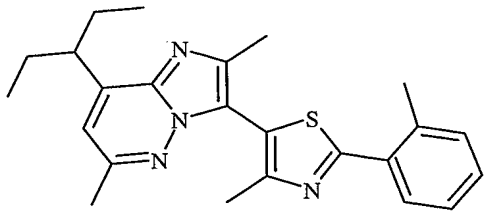
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(2,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 2,4-difluorophenyl boronic acid produces the title compound in 76% yield. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.370-8.310 (m, 1H); 7.586-7.540 (m, 1H); 7.36-7.32 (m, 1H); 7.054 (s, 1H); 3.14-3.13 (m, 1H); 2.492 (s, 3H); 2.391 (s, 3H); 2.345 (s, 3H); 1.906-1.797 (m, 4H); 0.826-0.788 (m, 6H) ppm.

Example 15.

Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(o-tolyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

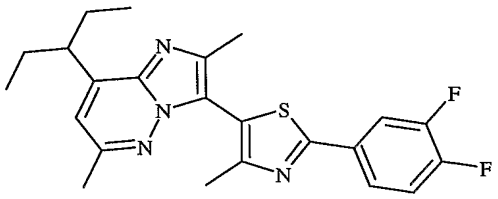


Using a procedure similar to Example 8, o-tolyl boronic acid produces the title compound in 87% yield where the crude mixture is purified by silica gel chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 405.2 (M+1); ^{1}H-

NMR (DMSO-d6) = 7.857-7.838 (d, 1H); 7.429-7.419 (d, 2H); 7.393-7.352 (m, 1H); 7.049 (s, 1H); 3.145-3.114 (m, 1H); 2.647 (s, 3H); 2.502 (s, 3H); 2.406 (s, 3H); 2.337 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 16.

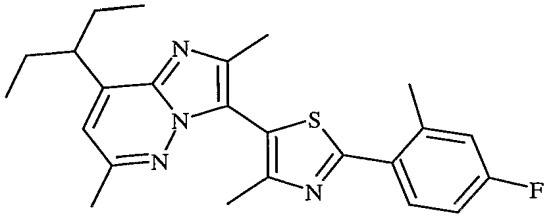
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(3,4-difluorophenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 3,4-difluorophenyl boronic acid produces the title compound in 74% yield where the crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. MS, ES+ = 427.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.07-8.02 (m, 1H); 7.849 (s, 1H); 7.66-7.59 (m, 1H); 7.062 (s, 1H); 3.12-3.11 (m, 1H); 2.498 (s, 3H); 2.392 (s, 3H); 2.319 (s, 3H) 1.905-1.779 (m, 4H); 0.826-0.790 (m, 6H) ppm.

Example 17.

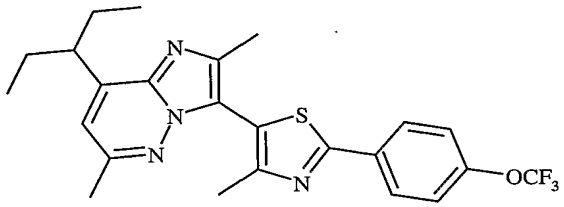
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-fluoro-2-methylphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 8, 4-fluoro-2-methylphenyl boronic acid produces the title compound 0.040g (37% yield). MS, ES+ = 423.2 (M+1); ^{1}H-NMR (DMSO-d6) = 7.918-7.882 (m, 1H); 7.323-7.241 (d, 1H); 7.234-7.192 (m, 1H); 7.049 (s, 1H); 3.142-3.111 (m, 1H); 2.650 (s, 3H); 2.499 (s, 3H); 2.401 (s, 3H); 2.330 (s, 3H); 1.905-1.779 (m, 4H); 0.969-0.788 (m, 6H) ppm.

Example 18.

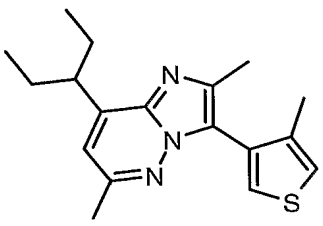
Preparation of 8-(1-ethyl-propyl)-3-[4-methyl-2-(4-trifluoromethoxyphenyl)-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a microwave pressure tube is added 0.100g (0.254mmol) of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 0.157g (0.762mmol) of 4-(trifluoromethoxy)benzene boronic acid, 0.147g (0.127mmol) of Pd(PPh3)4, 0.381mL (0.762mmol) of 2 M aqueous sodium carbonate, and 2mL Ethanol. The reaction mixture is heated in the microwave at 160°C for up to 1 hour. The reaction mixture is partitioned between 50 mL of ethyl acetate and 50 mL of water. The layers are separated and the aqueous is extracted 3X50mL of ethyl acetate, dried (MgSO4), and concentrated under vacuum. The crude mixture is purified by chromatography using 2% methanol in dichloromethane as a solvent system. The product containing fractions are combined to obtain 0.085g of the product, 70% yield. MS, ES+ = 475.2 (M+1); ^{1}H-NMR (DMSO-d6) = 8.134-8.112 (d, 2H); 7.553-7.532 (d, 2H); 7.059 (s, 1H); 3.142-3.113 (m, 1H); 2.500 (s, 3H); 2.399 (s, 3H); 2.330 (s, 3H); 1.907-1.782 (m, 4H); 0.827-0.791 (m, 6H) ppm.

Example 19.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

To a 250 mL round bottom flask is added 3-bromo-4-methyl-thiophene (5.00 g, 28.24 mmol), bis(pinacolato)diboron (7.89 g, 31.06 mmol) and KOAc (8.32 g, 84.72 mmol) in DMSO (85 mL). The mixture is degassed by bubbling N_2 for 5 min, $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ (1.15 g, 1.42 mmol) is added and the reaction mixture is heated to and stirred at 85 °C overnight. The reaction is cooled to rt, and diluted with EtOAc (400 mL), washed with H_2O (3 x 300 mL); dried with $MgSO_4$, filtered and concentrated. Purification of the crude material by chromatography to give the title compound (3.69 g, 16.5 mmol, 58%). ES-MS (m/z): calcd for $C_{11}H_{17}BO_2S$ (M^+): 224.1; found: 224.9.

B. 4-Methyl 3-thiophene boronic acid.

A solution of 4,4,5,5-tetramethyl-2-(4-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (3.69 g, 16.47 mmol) in acetone (30 mL) is treated with H_2O (30 mL), followed by $NaIO_4$ (7.05 g, 32.95 mmol). The resulting mixture is stirred at rt overnight. The organic solvent is removed in vacuo. The residue is diluted with H_2O (50 mL), extracted with EtOAc ((2 x 100 mL). The organic extracts are combined, dried with Na_2SO_4, filtered and concentrated. Purification of the crude material by chromatography gives the title compound (0.82 g, 5.78 mmol, 35%). ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 2.64-2.66 (m, 2H), 7.00-7.02 (m, 1H), 8.27 (d, J = 3.0 Hz, 1H). ES-MS (m/z): calcd for $C_5H_7BO_2S$ $(M-H)^-$: 141.0; found: 141.1.

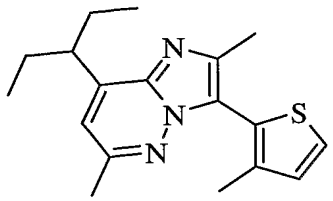
C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

To a 100 mL round bottom flask containing 4-methyl 3-thiophene boronic acid (0.27 g, 1.91 mmol), and 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.65 g, 1.91 mmol) in 20 mL of a stock solution (DME:H_2O:EtOH = 7:3:2) is added 2 M Na_2CO_3 (1.9 mL). The resulting mixture is degassed by bubbling N_2 for 5 min. Then $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) is added. The reaction mixture is refluxed overnight. The reaction is diluted with H_2O (20 mL); extracted with EtOAc (3 x 30 mL); dried (Na_2SO_4), filtered and purification of the crude material by chromatography gives the title compound (0.52 g, 1.66 mmol, 87%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz,

6H), 1.75-1.90 (m, 4H), 2.13 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.30-3.39 (m, 1H), 6.64 (s, 1H), 7.08-7.11 (m, 1H), 7.34 (d, J = 3.1 Hz, 1H). ES-MS (m/z): calcd for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.5; found: 314.2.

Example 20.

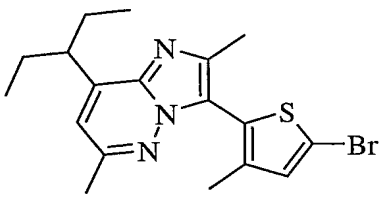
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To mixture of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (12.0 g, 34.96 mmol) and $PdCl_2$(dppf) (1.28 g, 1.75 mmol) is added a 0.5 M solution of 3-methyl-2-thienylzinc bromide in THF (100 mL, 50.0 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (500 mL), washed with 10% citric acid (500 mL), water (400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-20% EtOAc/hexane gradient) furnish the title compound (8.83 g, 28.17 mmol, 81%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.78-1.95 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.33-3.43 (m, 1H), 6.69 (s, 1H), 7.06 (d, J = 4.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.6; found: 314.2.

Example 21.

Preparation of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

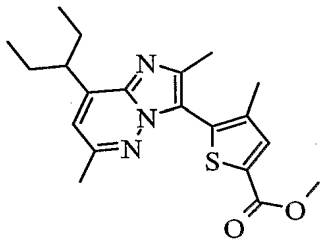


To a solution of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (8.83 g, 28.17 mmol) and CH_2Cl_2 (90 mL) is added NBS (5.26

g, 29.58 mmol). The solution is stirred at ambient temperature for 2 hours. The solution is washed with water (3 X 75 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (10.5 g, 26.76 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.3 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.68 (s, 1H), 6.98 (d, J = 4.9 Hz, 1H) ppm. LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.6; found: 392.1, 394.1.

Example 22.

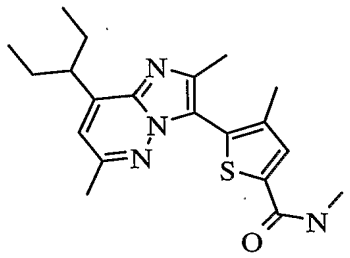
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.00 g, 2.66 mmol) in CH_3OH (12 mL), DMSO (18 mL), Et_3N (2.0 mL) with $Pd(OAc)_2$ (0.12 g, 0.538 mmol), dppf (0.937 g, 1.69 mmol) is reacted at CO atmosphere (100 psi) at 80 °C for 24 h. The reaction mixture is diluted with EtOAc (200 mL), washed with 0.1 M HCl (2 x 50 mL), brine (50 mL); dried with Na_2SO_4; filtered through silica gel and eluted with excess EtOAc. Purification of the crude material by chromatography gives the title compound (0.79 g, 2.12 mmol, 80%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.7 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.32-3.42 (m, 1H), 3.91 (s, 3H), 6.72 (s, 1H), 7.73 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{25}N_3O_2S$ $(M+H)^+$: 372.5; found: 372.2.

Example 23.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.



A. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid.

A solution of (1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methyl ester (0.78 g, 2.10 mmol) in CH_3OH (10 mL) is treated with 5.0 M NaOH (2.1 mL, 10.5 mmol). The resulting reaction mixture is refluxed for 4 h. Organic solvent is removed in vacuo; the aqueous residue is acidified by the addition of 2.0 M HCl to pH 5~6; it is then extracted with EtOAc (3 x 50 mL); dried (Na_2SO_4); filtered and concentration to give the title compound (0.74 g, 2.07 mmol, 98%). ^{1}H NMR (DMSO-d6): δ 0.79 (t, J = 7.6 Hz, 6H), 1.75-1.86 (m, 4H), 2.06 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.06-3.14 (m, 1H), 7.01 (s, 1H), 7.68 (s, 1H), 13.1 (bs, 1H). ES-MS (m/z): calcd for $C_{19}H_{23}N_3O_2S$ $(M+H)^+$: 358.5; found: 358.2.

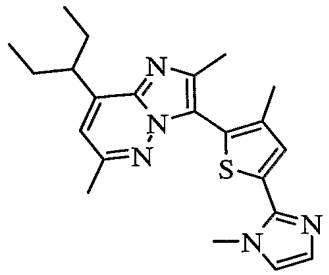
B. 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid methylamide.

5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (0.17 g, 0.47 mmol) is reacted with 2.0 M oxalyl chloride in CH_2Cl_2 (3.0 mL) at rt for 1h. The excess reagent and solvent are removed in vacuo. The residue is dissolved in CH_2Cl_2 (3mL), cooled to 0 °C and treated with 2.0 M methyl amine in THF (3 mL). The reaction is stirred at 0 °C for 10 min and rt for 30min. It is diluted with EtOAc (50 mL), washed with H_2O (15 mL0, 0.1 M NaOH (2 x 30 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the crude material by chromatography to give the title compound (0.91g, 0.25 mmol, 53%). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 6H), 1.75-1.91 (m, 4H), 2.14 (s, 3H), 2.47 (s, 3H), 2.52 (s, 3H), 3.02

(d, J = 4.8 Hz, 3H), 3.28-3.36 (m, 1H), 5.90-6.01 (m, 1H), 6.69 (s, 1H), 7.43 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{26}N_4OS$ $(M+H)^+$: 371.5; found: 371.2.

Example 24.

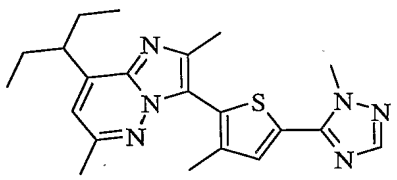
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-imidazol-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo-[*1,2-b*]pyridazine (0.98 g, 2.51 mmol) and 1-methyl-*1H*-imidazole (0.2 mL), $Pd(OAc)_2$ (34 mg, 0.15 mmol), PPh_3 (79 mg, 0.299 mmol), Cs_2CO_3 (1.95 g, 6.0 mmol) in DMF (50 mL) is stirred under N_2 at 130-140°C overnight. The reaction mixture is cooled, diluted with EtOAc (300 mL), washed with H_2O (3 x 100 mL); dried (Na_2SO_4); filtered and concentrated. Purification of the resulting crude material by chromatography yields the title compound (0.51 g, 1.29 mmol, 51%). ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 7.5 Hz, 6H), 1.77-1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 3.30-3.40 (m, 1H), 3.81 (s, 3H), 6.69 (s, 1H), 7.02 (s, 1H), 7.24 (s, 1H), 7.52 (s, 1H). ES-MS (m/z): calcd for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.6; found: 394.3.

Example 25.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

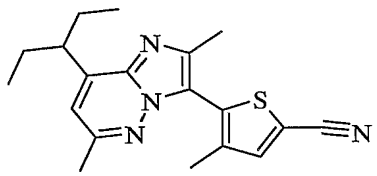


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.15 mL, 2.04 mmol) and THF (3 mL) is added a 1.34 M solution of n-Bu-Li in hexanes (1.60 mL, 2.14 mmol) over 20

minutes, then stirred at –78 °C for 1.5 hours. A 0.5 M solution of $ZnCl_2$ in THF (4.28 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.019 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution heated at 65 °C overnight diluted with CH_2Cl_2 (30 mL). The organic layer is washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%-60% EtOAc/hexane gradient). The residue is dissolved in Et_2O, treated with Darco®-60 for 15 minutes, dried with Na_2SO_4, and filtered to furnish the title compound (0.24 g, 0.61 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.20 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.37 (m, 1H), 4.14 (s, 3H), 6.69 (s, 1H), 7.45 (s, 1H), 7.87 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.6; found: 395.2.

Example 26.

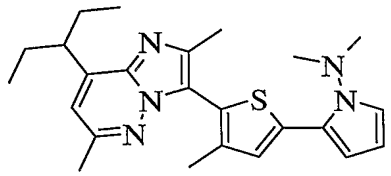
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile.



A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.28 mmol), DMF (5 mL), and $Zn(CN)_2$ (0.090 g, 0.76 mmol) is degassed with nitrogen for 15 minutes. $Pd(PPh_3)_4$ (0.74 g, 0.064 mmol) and the solution heated at 100 °C overnight. The solution is diluted with EtOAc (50 mL), washed with 2 M NH_4OH (2 X 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15% - 20% EtOAc/hexane gradient) furnish the title compound (0.39 g, 1.15 mmol, 91%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.15 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 3.26-3.34 (m, 1H), 6.72 (s, 1H), 7.53 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{22}N_4S$ $(M+H)^+$: 339.6; found: 339.2.

Example 27.

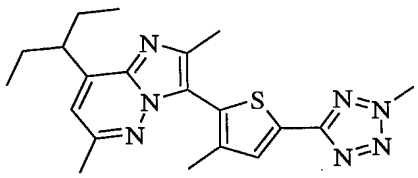
Preparation of (2-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.



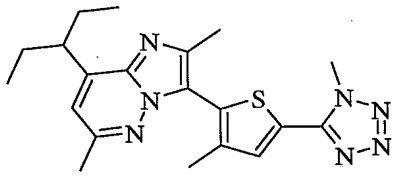
To a 0 °C solution 1-(dimethylamino)-pyrrole (0.24 mL, 2.04 mmol) and THF (4 mL) is added 1.24 M *n*-BuLi (1.73 mL, 2.14 mmol). The solution is warmed to ambient temperature and stirred for two hours. 0.5 M $ZnCl_2$ (4.28 mL, 2.14 mmol) is added and the solution is stirred for one hour. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and the solution is heated at 65 °C overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -20% EtOAc gradient) furnish the title compound (0.41 g, 0.97 mmol, 95%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.11 (s, 3H), 2.51 (s, 6H), 2.83 (s, 6H), 3.29-3.39 (m, 1H), 6.18-6.21 (m, 1H), 6.35 (dd, J = 4.0, 1.8 Hz, 1H), 6.65 (s, 1H), 6.98 (dd, J = 4.0, 1.8 Hz, 1H), 7.25 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{31}N_5S$ $(M+H)^+$: 422.2; found: 422.4.

Example 28 and 29.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.



Ex 28.



Ex. 29.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

To a solution of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carbonitrile (0.25 g, 0.74 mmol) and DMF (2.5 mL) is added Et_3N•HCl (0.31 g, 2.22 mmol) and NaN_3 (0.14 g, 2.20 mmol). The solution is heated at 100 °C overnight. The solution is diluted with water (20 mL) and extracted with EtOAc (3 X 15 mL), the combined organic layers are washed with 0.1 M HCl (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is recrystalized from acetonitrile furnish the title compound (0.14 g, 0.37 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.81 (t, J = 7.5 Hz, 6H), 1.66-1.87 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.26-3.35 (m, 1H), 6.83 (s, 1H), 7.84 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{23}N_7S$ $(M+H)^+$: 382.6; found: 382.2.

B. 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-2,5-dihydro-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-tetrazol-5-yl)-thiophen-2-yl]-imidazo[1,2 b]pyridazine.

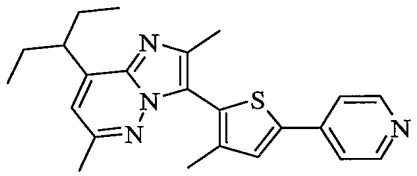
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1H-tetrazol-5-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.14 g, 0.35 mmol) and THF (3 mL) is added Et_3N (0.1 mL, 0.71 mmol) and MeI (0.024 mL, 0.39 mmol). The solution is stirred overnight, diluted with EtOAc (20 mL), washed with water (15 mL), 0.1 M HCl (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%- 40% EtOAc/hexane gradient) furnish Ex. 28 (0.71 g, 0.18 mmol, 51%), and Ex. 29 (0.031 g, 0.078 mmol, 22%).

Ex. 28: ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.75-1.92 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.28-3.38 (m, 1H), 4.38 (s, 3H), 6.68 (s, 1H), 7.71 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Ex. 29: ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.73-1.94 (m, 4H), 2.23 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.37 (m, 1H), 4.30 (s, 3H), 6.62 (s, 1H), 7.63 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{25}N_7S$ $(M+H)^+$: 396.6; found: 396.3.

Example 30.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-(5-Boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a -78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.20 g, 3.06 mmol) and THF (10 mL) is added 1.30 M *n*-Bu-Li (2.47 mL, 3.21 mmol) drop wise. The solution is stirred at –78 °C for one hour. $B(OMe)_3$ (0.38 mL, 3.65 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hours. 1 M HCl is added and the solution stirred for 10 minutes extracted with CH_2Cl_2 (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.47 g, 1.32 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.71-1.98 (m, 4H), 2.02 (s, 3H), 2.64 (s, 3H), 2.69 (s, 3H), 3.64-3.83 (m, 1H), 7.06 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{24}BN_3O_2S$ $(M+H)^+$: 358.4; found: 358.2.

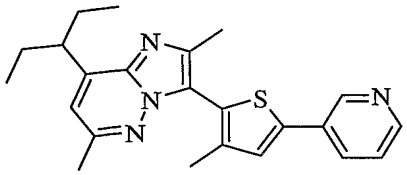
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

A solution of 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.70 mmol), 4-bromopyridine hydrochloride (0.16 g, 0.84 mmol), and 2 M Na_2CO_3 (0.87 mL, 1.75 mmol) and *n*-PrOH (2.5 mL) is degassed with nitrogen for 10 minutes. $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol) is added and the solution heated at 85 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.41 mmol, 59%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.52 (s,

3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.43 (s, 1H), 7.52 (d, J = 5.5 Hz, 2H), 8.62 (d, J = 5.5 Hz, 2H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2 found: 391.2.

Example 31.

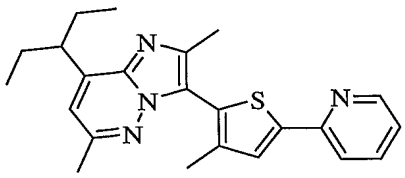
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol), and THF (5 mL) is added 1.34 M *n*-Bu-Li (1.0 mL, 1.34 mmol). The solution is stirred for at -78 °C for 30 minutes and 0.5 M $ZnCl_2$ in THF (2.7 mL, 1.34 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 3-bromopyridine (0.15 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with CH_2Cl_2 (40 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) concentrated and re-dissolved in Et_2O. The solution is treated with Darco®-60 for 15 minutes, dried over Na_2SO_4, and filtered thru celite® furnish the title compound (0.26 g, 0.67 mmol, 52%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.26-7.32 (m, 2H), 7.86 (dt, J = 7.9, 1.8 Hz, 1H), 850 (d, J = 3.2 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 32.

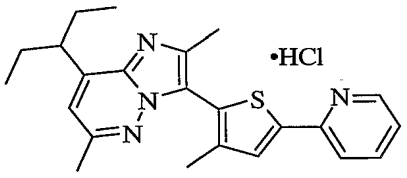
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a mixture of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide in THF (5.1 mL, 2.55 mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with 10% citric acid (50 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.45 g, 1.15 mmol, 89%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.52 (s, 6H), 3.30-3.39 (m, 1H), 6.67 (s, 1H), 7.12-7.16 (m, 1H), 7.53 (s, 1H), 7.63-7.71 (m, 2H), 8.57 (dt, J = 1.3, 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.6; found: 391.2.

Example 33.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine hydrochloride.

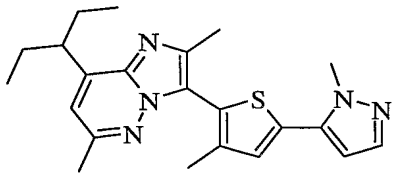


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.15 g, 38 mmol) and MeOH (2 mL) is added AcCl (0.028 mL, 0.39 mmol). After one hour the solution is concentrated and the residue recrystalized from EtOAc/ hexane furnish the title compound (0.11 g, 0.26 mmol, 69%). ^{1}H NMR ($CDCl_3$), δ 0.97 (t, J = 7.4 Hz, 6H), 1.75-2.03 (m, 4H), 2.17 (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 3.86-3.98 (m, 1H), 7.17 (s, 1H), 7.21-7.30 (m, 2H), 7.62 (bs, 1H), 7.67-

7.7.82 (m, 2H), 8.60 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}ClN_5S$ $(M+H)^+$: 428.1; found: 391.2.

Example 34.

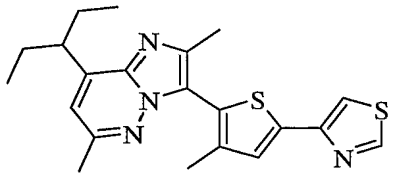
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-*2H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 1-methylpyrazole (0.17 g, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.35 g, 0.89 mmol, 88%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.28-3.38 (m, 1H), 4.05 (s, 3H), 6.42 (d, J = 1.8 Hz, 1H), 6.68 (s, 1H), 7.08 (s, 1H), 7.46 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.7; found: 394.2.

Example 35.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

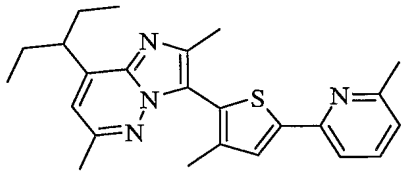


Using a procedure similar to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40 g, 1.02 mmol), 1.34 M *n*-Bu-Li (0.8 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-thiazole (0.20 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16g, 0.40 mmol, 40%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.4 Hz, 6H), 1.70-1.96 (m, 4H), 2.17 (s, 3H), 2.64 (s, 3H), 2.66 (s, 3H), 3.38-3.48 (m, 1H), 7.16 (d, J = 1.8

Hz, 1H), 7.44 (s, 1H), 7.51 (d, J = 1.8 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.2.

Example 36.

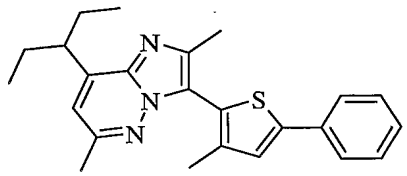
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and $PdCl_2$(dppf) (0.056 g, 0.076 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (6.0 mL, 3.06 mmol) furnish the title compound (0.29 g, 0.72 mmol, 47%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 2.58 (s, 3H), 3.31-3.40 (m, 1H), 6.67 (s, 1H), 7.00 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 8.56 (t, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.7; found: 405.2.

Example 37.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-phenyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

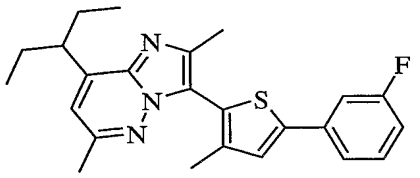


Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.05 g, 0.069 mmol) and 0.5 M solution of phenylzinc iodide in THF (5.5 mL, 2.76 mmol) furnish the title compound (0.25 g, 0.64 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.52 (s, 3H), 2.53 (s,

3H), 3.31-3.41 (m, 1H), 6.68 (s, 1H), 7.26 (s, 1H), 7.27-30 (m, 1H), 7.35-7.41 (m, 2H), 7.61-7.66 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.3; found: 390.3.

Example 38.

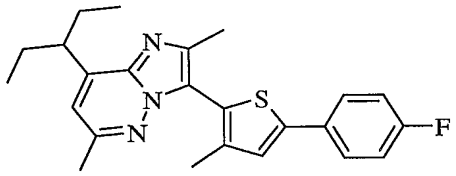
Preparation of 8-(1-ethyl-propyl)-3-[5-(3-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.063 mmol) and 0.5 M solution of 3-flourophenylzinc iodide in THF (5.1 mL, 2.55 mmol) furnish the title compound (0.24 g, 0.59 mmol, 46%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.31-3.39 (m, 1H), 6.69 (s, 1H), 6.94-7.01 (m, 1H), 7.26 (s, 1H), 7.30-7.42 (m, 3H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.2.

Example 39.

Preparation of 8-(1-ethyl-propyl)-3-[5-(4-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

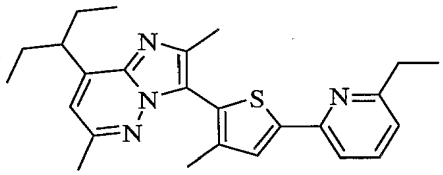


A slurry of 0.05 g/mL of Reike® Zn in THF (0.26 g, 4.01 mmol) and 1-bromo-4-fluoro-benzene (0.29 mL, 2.68 mmol) is heated at a reflux overnight. The solution is filtered under nitrogen. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol) and $PdCl_2$(dppf) (0.033 g, 0.045 mmol) are added, and the solution is heated at a reflux overnight diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column

chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.091 g, 0.22 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.38 (m, 1H), 6.68 (s, 1H), 7.08 (d, J = 8.8 Hz, 2H),7.18 (s, 1H), 7.59 (dd, J = 8.5, 5.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.7; found: 408.3.

Example 40.

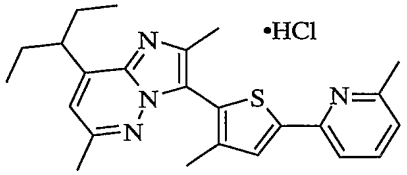
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-ethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, 2-bromo-6-ethyl pyridine (0.26 g, 1.41 mmol), 1.56 M *n*-Bu-Li (0.94 mL, 1.47 mmol), 0.5 M $ZnCl_2$ in THF (3.0 mL, 1.53 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) produce the title compound (0.15 g, 0.36 mmol, 28%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.34 (t, J = 7.5 Hz, 3H), 1.75-1.94 (m, 4H), 2.16 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 2.85 (q, J = 16.2, 7.5 Hz, 2H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 8.59 (t, J = 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.3; found: 419.3.

Example 41.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine hydrochloride.

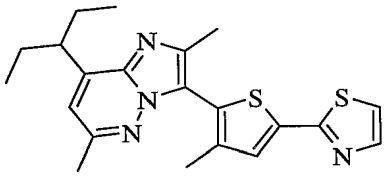


Using a procedure similar to Example 33, 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36

mmol), MeOH (6 mL) and AcCl (0.098 mL, 1.36 mmol) furnish the title compound (0.11 g, 0.25 mmol, 42%). ^{1}H NMR ($CDCl_3$), δ 0.96 (t, J = 7.2 Hz, 6H), 1.74-1.89 (m, 2H), 1.89-2.02 (m, 2H), 2.22 (s, 3H), 2.68 (s, 3H), 2.78 (s, 3H), 3.08 (s, 3H), 3.88-3.98 (m, 1H), 7.23 (s, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.06 (s, 1H), 8.82 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{29}ClN_4S$ $(M+H)^+$: 441.3; found: 405.2.

Example 42.

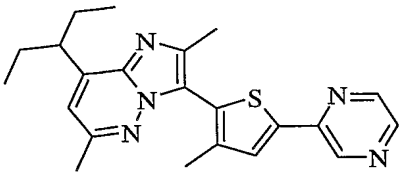
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 g, 1.17 mmol), 0.5 M 2-thiazolylzinc bromide in THF (4.7 mL, 2.35 mmol) and $PdCl_2$(dppf) (0.043 g, 0.059 mmol) furnish the title compound (0.32 g, 0.81 mmol, 70%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 7.70 (s, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 7.78 (d, J = 3.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.7; found: 397.1.

Example 43.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrazin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

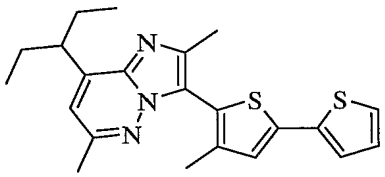


Using a procedure similar to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) (example Rupp-2), 2-chloropyrazine (0.11 mL, 1.22 mmol), 1.42 M *n*-Bu-Li (1.52 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051

mmol) furnish the title compound (0.19 g, 0.49 mmol, 48%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.20 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.63 (s, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.51 (t, J = 1.9 Hz, 1H), 8.96 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 44.

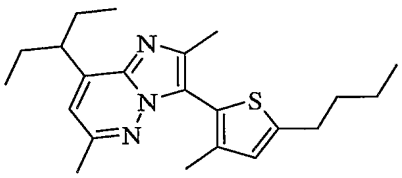
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 0.5 M 2-thiophenlyzinc bromide in THF (3.0 mL, 1.53 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) furnish the title compound (0.25g, 0.63 mmol, 83%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.14 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.02 (dd, J = 5.0, 3.6 Hz, 1H), 7.11 (s, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.19 (dd, J = 5.0, 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_3S_2$ $(M+H)^+$: 396.7; found: 396.2.

Example 45.

Preparation of 3-(5-butyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

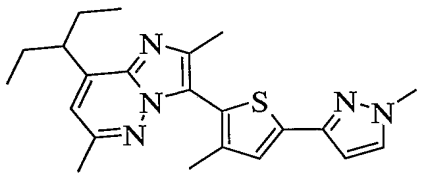


Using a procedure similar to Example 25 from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.1.02 mmol), 1.34 M *n*-Bu-Li (1.60 mL, 2.14 mmol), 0.5 M $ZnCl_2$ (4.3 mL, 2.14 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.25g, 0.69 mmol, 68%). ^{1}H NMR

($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 0.97 (t, J = 7.5 Hz, 3H), 1.40-1.51 (m, 2H), 1.67-1.92 (m, 6H), 2.07 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 3.30-3.38 (m, 1H), 6.64 (s, 1H), 6.70 (s, 1H) LC/MS (m/z): calcd. for $C_{22}H_{31}N_3S$ $(M+H)^+$: 370.3; found: 370.2.

Example 46.

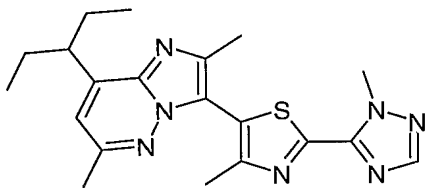
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-bromo-1-methyl-*1H*-pyrazole (Pavlik, J.; Kurzweil, E.; *J. Org. Chem.,* 1991, 56, 22, 6313) (0.20 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.041g, 0.10 mmol, 10%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 3.95 (s, 3H), 6.47 (d, J = 2.2 Hz, 1H), 6.67 (s, 1H), 7.25 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 47.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.

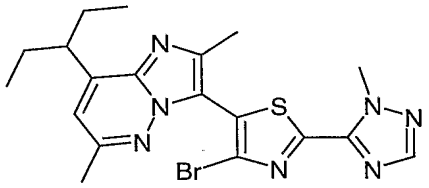


82 mg of 1-Methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78C to room temperature for 10min and cooled to –78°C

again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78C to room temperature for 15 min. 265 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.66 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2 days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH=10:2:1) to give 57 mg of the title product. Yield 22%. mass spectrum (m/e):396(M+1). ^{1}H-NMR (CDCl3): δ 7.96 (s, 1H), 6.77 (s, 1H), 4.45 (s, 3H), 3.36 (m, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.47 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.3Hz, 6H).

Example 48.

Preparation of 3-[4-bromo-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

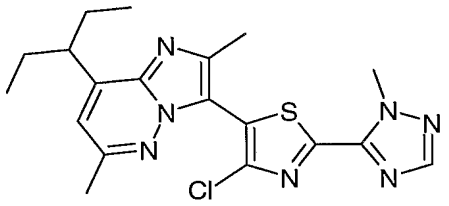


82 mg of 1-methyl-1,2,4-triazole (0.99 mmol) is dissolved in 2 ml of dry THF and cooled to –78°C and 0.4 ml of n-butyllithium 2.5 M in hexane (0.99 mmol) is added. The reaction mixture is stirred at –78°C to room temperature for 10min and cooled to –78°C again. 1.98 ml of 0.5 M zinc chloride 0.5 M solution in THF (0.99 mmol) is added and stirred at –78°C to room temperature for 15min. 152 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.33 mmol) and 27 mg of PdCl2(dppf) (0.033 mmol) are added and the vial is capped with a Teflon cap and heated at 80°C for 2days. The reaction is cooled to room temperature and quenched with sat. NH4Cl and extracted with CH2Cl2. The separated CH2Cl2 layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2M NH3 in MeOH=10:2:1) to give 88mg of the title product. Yield 54%.

mass spectrum (m/e):461(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.77 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 2.55 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 49.

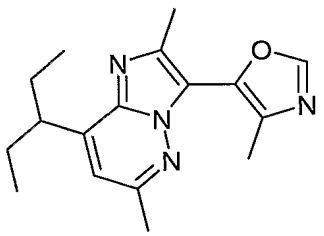
Preparation of 3-[4-chloro-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



175 mg of 3-[4-Bromo-2-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.38 mmol) and 56 mg of copper chloride (0.57 mmol) are placed into 4 ml vial with 3.0 ml of dry DMF and the vial is capped with a Teflon cap. The vial is heated at 130°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and hexane:AcOEt=8:1) to give 91 mg of crude product. The pure product is recrystalized from Et2O/Hexane. 73 mg (46%). mass spectrum (m/e):416(M+1). ^{1}H-NMR (CDCl3): 7.98 (s, 1H), 6.80 (s, 1H), 4.44 (s, 3H), 3.35 (m, 1H), 2.59 (s, 3H), 1.88 (m, 4H), 0.92 (t, J=7.5Hz, 6H).

Example 50.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine.

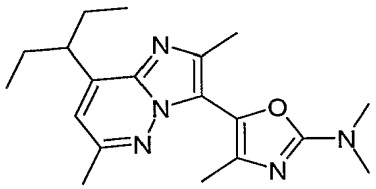


686 mg of 8-(1-Ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 mmol), 830 mg of 4-methyl-oxazole. (10 mmol), 105 mg of triphenylphosphine (0.4 mmol) and 1.30 g of cesium carbonate (4.0 mmol) are placed into tube with 10 ml of dry

DMF. N2 gas is bubbled in for 20min and 92 mg of Pd2dba3 (0.1 mmol) is added. The tube is sealed and heated at 130°C overnight. After being cooled to room temperature, water and CHCl2 are added to the mixture. The CHCl2 layer is separated, washed with sat. NaCl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 234 mg of the title product. Yield 39%. mass spectrum (m/e):299(M+1). ^{1}H-NMR (CDCl3): 8.06 (s, 1H), 6.75 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.50 (s, 3H), 2.29 (s, 3H), 1.86 (m, 4H), 0.90 (t, J=7.4Hz, 6H).

Example 51.

Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.



A. 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

230 mg of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-methyl-oxazol-5-yl)-imidazo[*1,2-b*]pyridazine (0.77 mmol) is dissolved in 20 ml of CH2Cl2 and 178 mg of NBS (1.0 mmol) is added. The reaction mixture is stirred at room temperature overnight. The reaction mixture is washed with sat. Na2S2O3, sat. NaCl, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 36 mg of the title compound. Yield 12%. mass spectrum (m/e):378(M+1). ^{1}H-NMR (CDCl3): 6.82 (s, 1H), 3.39 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.26 (s, 3H), 1.85 (m, 1H), 0.89 (t, J=7.4Hz, 6H).

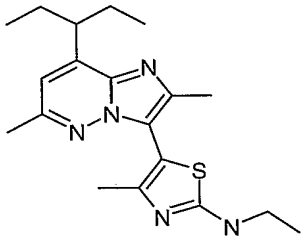
B. N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-oxazol-2-yl}-dimethylamine.

32 mg of 3-(2-Bromo-4-methyl-oxazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.08 mmol) and 78 mg of cesium carbonate (0.24 mmol) are placed into vial with 3 ml of dimethylamine 2.0 M in THF. The vial is capped with a

Teflon cap and heated at 110°C for 3days. The reaction mixture is cooled to room temperature, concentrated, and applied onto a silica-gel chromatography column (Hexane :AcOEt:2M NH3 in MeOH=10:2:1) to give 24 mg of the title product. Yield 89%. mass spectrum (m/e):342(M+1). ^{1}H-NMR (CDCl3): 6.71(s, 1H), 3.34 (m, 1H), 3.13 (s, 6H), 2.56 (s, 3H), 2.49 (s, 3H), 2.14 (s, 3H), 1.84 (m, 4H), 0.89 (t, J=7.5Hz, 6H).

Example 52.

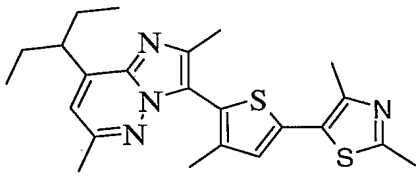
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[(4-methyl-2-ethylamino)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



The title compound is prepared essentially as described in Example 51B. employing 2.0 ml of ethylamine 2.0 M in THF and 182 g of cesium carbonate (0.56 mmol), 78%. mass spectrum (m/e):358 (M+1); 1H-NMR (CDCl3): 6.69(s, 1H), 5.23(br, 1H), 3.38(m, 3H), 2.56(s, 3H), 2.46(s, 3H), 2.17(s, 3H), 1.85(m, 4H), 1.35(t, 3H, J=7.2Hz), 0.90(t, 6H, J=7.2Hz).

Example 53.

Preparation of 3-[5-(2,4-dimethyl-thiazol-5-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

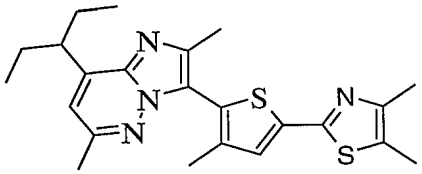


To a –78 °C mixture of 2,4-dimethylthiazole (0.23 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.09 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-

2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (20 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (0%-15% EtOAc/hexane gradient) furnish the title compound (0.21 g, 0.49 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.14 (s, 3H), 2.49 (s, 3H), 2.52 (s, 3H), 2.57 (s, 3H), 2.66 (s, 3H), 3.28-3.38 (m, 1H), 6.68 (s, 1H), 7.00 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 54.

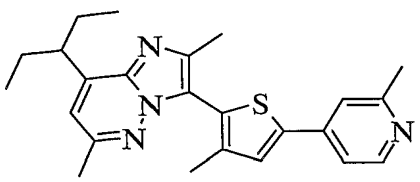
Preparation of 3-[5-(4,5-dimethyl-thiazol-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, from 4,5-dimethylthiazole (0.22 mL, 2.04 mmol), 1.56 M *n*-Bu-Li (1.34 mL, 2.09 mmol), $ZnCl_2$ (4.3 mL, 2.14 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.27 g, 0.64 mmol, 63%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.13 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 2.51(s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.32 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4S_2$ $(M+H)^+$: 425.3; found: 425.2.

Example 55.

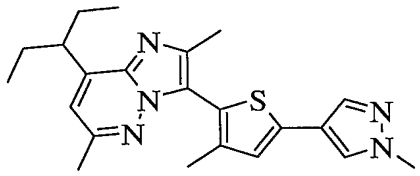
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(2-methyl-pyridin-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31, from 4-bromo-2-methyl pyridine (Fukaya et. el. *Chem. Pharm. Bull.*, 1990, 38, 2446) (0.21 g, 1.22 mmol), 1.56 M *n*-Bu-Li (0.69 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.2 mL, 1.12 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.058 g, 0.14 mmol, 14%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.16 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 2.58 (s, 3H), 3.27-3.37 (m, 1H), 6.68 (s, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 8.46 (t, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.2.

Example 56.

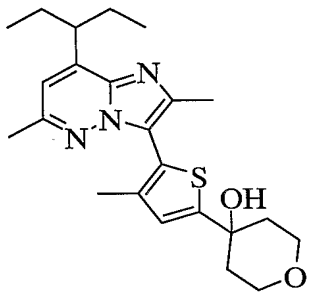
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-pyrazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 31, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.42 M *n*-Bu-Li (0.75 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 4-bromo-1-methyl-*1H*-pyrazole (0.25 g, 1.53 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnishes the title compound (0.092g, 0.23 mmol, 23%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 6H), 1.73-1.92 (m, 4H), 2.12 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 3.92 (s, 3H), 6.66 (s, 1H), 6.98 (s, 1H), 7.54 (s, 1H), 7.68 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 57.

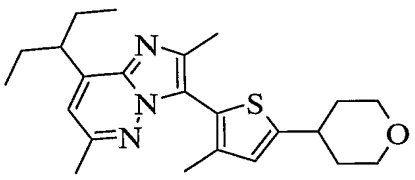
Preparation of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol.



To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.53 mmol) and THF (10 mL) is added 1.56 M *n*-Bu-Li (1.03 mL, 1.61 mmol). After 30 minutes tetrahydro-pyran-4-one (0.21 mL, 2.29 mmol) is added over 5 minutes. The solution is stirred at –78°C for 2 hours, warmed to ambient temperature, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-100% EtOAc/hexane gradient) furnish the title compound (0.38 g, 0.92 mmol, 60%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 1.91-2.00 (m, 2H), 2.11 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.51 (s, 3H), 3.30-3.39 (m, 1H), 3.83-3.98 (m, 5H), 6.66 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3O_2S$ $(M+H)^+$: 414.3; found: 414.2.

Example 58.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Method A.

To a solution of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-tetrahydro-pyran-4-ol (0.25 g, 0.604 mmol) and CH_2Cl_2

(10 mL) is added TFA (0.79 mL, 10.28 mmol) and Et_3SiH (0.25 mL, 1.57 mmol). The solution is concentrated, dissolved in EtOAc (30 mL), washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient), is dissolved in EtOH (25 mL), 10 % Pd/C (0.07 g, 0.066 mmol) is added and the solution stirred under an atmosphere of H_2. After 2 hours the solution is filtered thru celite® and concentrated. The residue is purified by ISCO column chromatography (30% EtOAc in hexane) furnish the title compound (0.033 g, 0.083 mmol, 14%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.95 (m, 4H), 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.20-2.30 (m, 2H), 2.46 (s, 3H), 2.52 (s, 3H), 3.00-3.11 (m, 1H), 3.30-3.40 (m, 1H), 3.54 (dt, J = 11.8, 2.2 Hz, 2H), 4.08 (dd, J = 11.8, 2.2 Hz, 2H), 6.65 (s, 1H), 6.75 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{31}N_3OS$ $(M+H)^+$: 398.7; found: 398.2.

Method B.

A. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol.

To a -78°C solution of 2-bromo-3-methyl-thiophene (2.0 g, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.32 mL, 18.63 mmol). After 30 minutes at –78°C tetrahydro-pyran-4-one (2.3 mL, 23.07 mmol) is added and the solution is warmed to ambient temperature. The solution is washed with sat. NH_4Cl (30 mL). The aqueous phases is extracted with EtOAc. The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (30%-100% EtOAc/hexane gradient) furnish the title compound (2.3 g, 8.30 mmol, 47%). ^1H NMR ($CDCl_3$), δ 1.82 (m, 2H), 2.00 (s, 3H), 2.06-2.15 (m, 3H), 2.16 (s, 3H), 3.77-3.84 (m, 2H), 3.87 dt, J = 11.3, 2.2 Hz, 2H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{13}BrO_2S$ $(M+H)^+$: 277.0; found: 260.9.

B. 4-(5-Bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran.

To a solution of 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydro-pyran-4-ol (2.3 g, 8.30 mmol) and 1,2-dichloroethane (50 mL) is added ZnI_2 (3.97 g, 12.45 mmol) and sodium cyanoborohydride (3.91, 62.23 mmol). The solution is stirred for 1 hour, filtered

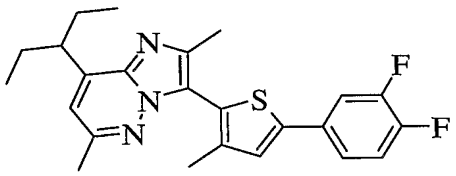
thru celite and concentrated. The residue is purified by ISCO column chromatography (5%-10% EtOAc/hexane gradient) furnish the title compound (1.53 g, 5.86 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 1.69-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.14 (s, 3H), 2.84-2.98 (m, 1H), 3.49 (dt, J = 11.8, 2.2 Hz, 2H), 4.00-4.07 (m, 2H), 6.51 (s, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(tetrahydro-pyran-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 4-(5-bromo-4-methyl-thiophen-2-yl)-tetrahydropyran (0.83 g, 3.19 mmol), 1.56 M *n*-Bu-Li (2.04 mL, 3.19 mmol), $ZnCl_2$ (6.4 mL, 3.19 mmol), 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.56 mmol) and $Pd(PPh_3)_4$ (0.092 g, 0.008 mmol) furnish the title compound (0.072 g, 0.18 mmol, 11%). Spectrum identical to that from Method A.

Example 59.

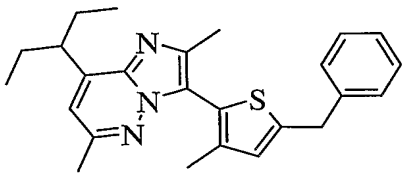
Preparation of 3-[5-(3,4-difluoro-phenyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 1.27 mmol) and $PdCl_2$(dppf) (0.047 g, 0.064 mmol) and 0.5 M solution of 3,4-difluorophenylzinc bromide in THF (5.1 mL, 2.55 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-80% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.18 g, 0.42 mmol, 33%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 3.31-3.40 (m, 1H), 6.69 (s, 1H), 7.13-7.21 (m, 1H), 7.18 (s, 1H), 7.31-7.36 (m, 1H), 7.39-7.46 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_2N_3S$ $(M+H)^+$: 426.3; found: 426.2.

Example 60.

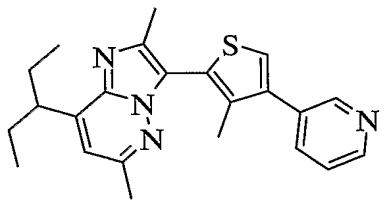
Preparation of 3-(5-benzyl-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of benzylzinc bromide in THF (4.6 mL, 2.29 mmol) are reacted. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 40-65% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.062 g, 0.15 mmol, 20%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.51 (s, 3H), 3.29-3.39 (m, 1H), 4.16 (s, 2H), 6.65 (s, 1H), 6.68(s, 1H), 7.22-7.29 (m, 1H), 7.31-7.36 (m, 4H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.2.

Example 61.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-pyridin-3-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.

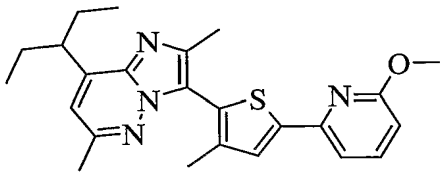


A solution of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.64 mmol), pyridine-3-boronic acid (0.086 g, 0.70 mmol), 2 M Na_2CO_3 (0.48 mL, 0.96 mmol) and, *n*-PrOH (3 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (2.7 mg, 0.0013 mmol) and PPh_3 (0.010 g, 0.038 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (30 mL), washed with 10% Na_2CO_3 (30 mL), water (30 mL), brine (30 mL),

dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO (20-40% EtOAc gradient) furnish the title compound (0.051 g, 0.13 mmol, 20%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.09 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.29-3.40 (m, 1H), 6.69 (s, 1H), 7.33-7.43 (m, 1H), 7.47 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 8.61 (bs, 1H), 8.78 (bs, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4S$ $(M+H)^+$: 391.2; found: 391.4.

Example 62.

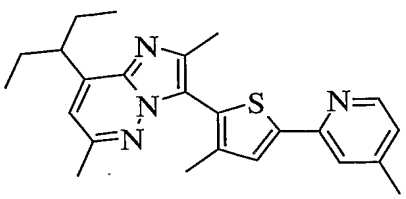
Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methoxy-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 6-methoxy-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.12 g, 0.29 mmol, 38%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.15 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 3.98 (s, 3H), 6.61 (d, J = 7.5 Hz, 1H), 6.70(s, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 63.

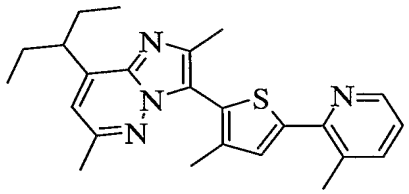
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(4-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.21 g, 0.52 mmol, 68%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.52 (s, 6H), 3.30-3.40 (m, 1H), 6.67 (s, 1H), 6.97(d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.52 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 64.

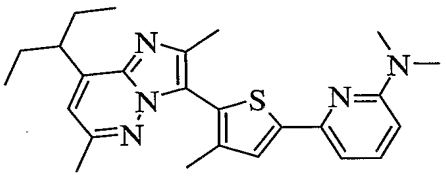
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 3-methyl-2-pyridylzinc bromide in THF (5.0 mL, 2.50 mmol) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 2.63 (s, 3H), 3.29-3.39 (m, 1H), 6.67 (s, 1H), 7.06-7.14 (m, 1H), 7.44 (s, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 8.47 (dd, J = 4.9, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 65.

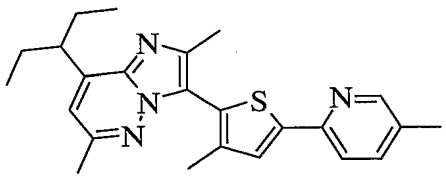
Preparation of (6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-dimethyl-amine.



Using a procedure similar to Example 39, from Rieke® Zn in THF (0.20 g, 3.06 mmol), (6-bromo-pyridin-2-yl)-dimethyl-amine (Newkomw et. el. *J. Org. Chem.*, 1988, 3, 786) (0.41 mL, 2.04 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.35 g, 0.89 mmol), and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.16 g, 0.37 mmol, 36%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.15 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.21 (s, 6H), 3.30-3.40 (m, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 6.95 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 8.4, 7.4 Hz, 1H), 7.46 (s, 1H). LC/MS (m/z): calcd. for $C_{25}H_{31}N_5S$ $(M+H)^+$: 434.3; found: 434.3.

Example 66.

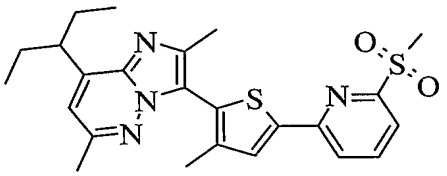
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.765 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol) and 0.5 M solution of 4-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.53 mmol) furnish the title compound (0.23 g, 0.57 mmol, 74%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.16 (s, 3H), 2.35 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.31-3.41 (m, 1H), 6.67 (s, 1H), 7.48(s, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 8.39-8.40 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.3; found: 405.3.

Example 67.

Preparation of 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-6-methanesulfonyl-pyridine.

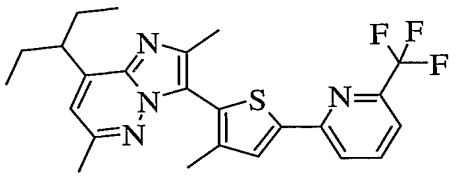
To a solution of 2-bromo-6-methylsulfanyl-pyridine (Testaferri et. el *Tetrahedron*, 1985, 41, 1373) (2.15 g, 10.53 mmol) and CH_2Cl_2 (30 mL) is added 56-87% mCPBA (12 g, 42.15 mmol). The solution is cooled with ice to ambient temperature and the solution is stirred for 2 hour, washed with sat. $Na_2S_2O_3$ (15 mL), sat. $NaHCO_3$ (2 X 15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by recrystalization from EtOAc /hexane furnish the title compound (1.71 g, 7.24 mmol, 69%). ^1H NMR ($CDCl_3$), δ 3.26 (s, 3H), 7.73 (dd, J = 8.0, 0.9 Hz, 1H), 7.82 (dd, J = 8.0, 7.5 Hz, 1H), 8.05 (dd, J = 7.5, 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_6H_6BrNO_2S$ $(M+H)^+$: 235.9; found: 235.9.

B. 8-(1-ethyl-propyl)-3-[5-(6-methanesulfonyl-pyridin-2-yl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2-bromo-6-methanesulfonyl-pyridine (0.29 mL, 1.22 mmol), 1.3 M *n*-Bu-Li (0.82 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.13 g, 0.28 mmol, 27%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.18 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30 (s, 3H), 3.30-3.38 (m, 1H), 6.70 (s, 1H), 7.64 (s, 1H), 7.83 (dd, J = 7.6, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.93 (dd, J = 7.9, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4O_2S_2$ $(M+H)^+$: 469.3; found: 469.2.

Example 68.

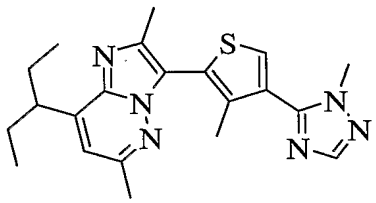
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 2-chloro-6-trifluoromethyl-pyridine (0.29 mL, 1.22 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.20 g, 0.44 mmol, 43%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.50 (dd, J = 7.5, 0.9 Hz, 1H), 7.65 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 69.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

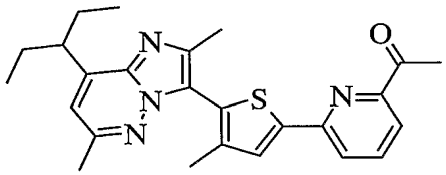


To a slurry of 0.05 g/ mL of Reike® Zn in THF (3.0 mL, 2.29 mmol) is added a solution of 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution was heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution was transferred to a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-152) (0.32 g, 0.70 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat.

NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (50%-100% Et_2O) to furnish the title compound (0.058 g, 0.15 mmol, 19%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.11 (s, 3H), 2.47 (s, 3H), 2.49 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.68 (s, 1H), 7.64 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6S$ $(M+H)^+$: 395.2; found: 395.4.

Example 70.

Preparation of 1-(6-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.



A. 3-[5-(6-Bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 25, 2,6-dibromo-pyridine (0.91 g, 3.82 mmol), 1.34 M *n*-Bu-Li (1.50 mL, 2.00 mmol), $ZnCl_2$ (4.0 mL, 2.00 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 1.92 mmol) and $PdCl_2$(dppf) (0.070 g, 0.096 mmol) furnish the title compound (0.26 g, 0.55 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.16 (s, 3H), 2.50 (s, 3H), 2.52 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.31 (dd, J = 7.5, 1.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.58 (s, 1H).

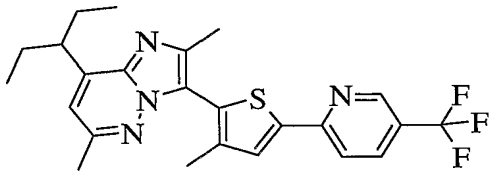
B. 1-(6-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-pyridin-2-yl)-ethanone.

To a –78°C solution of 3-[5-(6-bromo-pyridin-2-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine) (0.26 g, 0.55 mmol), and THF (5 mL), is added 1.34 M *n*-Bu-Li (0.43 mL, 0.58 mmol). After 30 minutes *N*-methoxy-*N*-methyl-acetamide (0.065 mL, 0.61 mmol) is added and the solution warmed to ambient

temperature. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15-20% EtOAc/hexane gradient) furnish the title compound (0.030 g, 0.069 mmol, 13%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.19 (s, 3H), 2.52 (s, 3H), 2.53 (s, 3H), 2.77 (s, 3H), 3.30-3.40 (m, 1H), 6.69 (s, 1H), 7.59 (s, 1H), 7.77-7.85 (m, 2H), 7.87 (dd, J = 6.8, 2.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{28}N_4OS$ $(M+H)^+$: 433.3; found: 433.2.

Example 71.

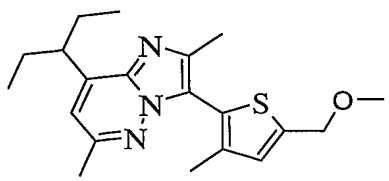
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-trifluoromethyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 2-bromo-5-trifluoromethyl-pyridine (2.14 mL, 1.07 mmol), 1.34 M *n*-Bu-Li (0.80 mL, 1.07 mmol), $ZnCl_2$ (2.14 mL, 1.07 mmol), 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.17 g, 0.37 mmol, 36%). ^1H NMR ($CDCl_3$), δ 0.90 (t, J = 7.3 Hz, 6H), 1.76-1.94 (m, 4H), 2.18 (s, 3H), 2.19 (s, 3H), 2.53 (s, 3H), 3.31-3.40 (m, 1H), 6.70 (s, 1H), 7.63 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 8.4, 2.2 Hz, 1H), 7.79-7.82 (m, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}F_3N_4S$ $(M+H)^+$: 459.3; found: 459.2.

Example 72.

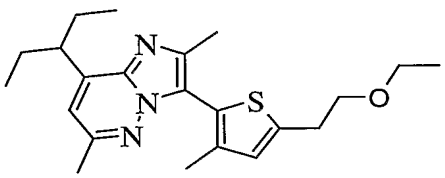
Preparation of 8-(1-ethyl-propyl)-3-(5-methoxymethyl-3-methyl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (3 mL) is added 1.34 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes iodo-methoxy-methane (0.097 mL, 1.15 mmol) is added and the solution warmed to ambient temperature. After 1 hour the solution is diluted with EtOAc (40 mL) washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.12 g, 0.34 mmol, 44%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.09 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.28-3.37 (m, 1H), 3.44 (s, 3H), 4.61 (s, 2H), 6.65 (s, 1H), 6.93 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{27}N_3OS$ $(M+H)^+$: 358.3; found: 358.3.

Example 73.

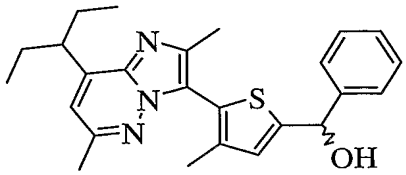
Preparation of 3-[5-(2-ethoxy-ethyl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 72, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 1.34 M *n*-Bu-Li (0.53 mL, 0.84 mmol), 1-bromo-2-ethoxy-ethane (0.13 mL, 1.15 mmol) and KI (0.013 g, 0.076 mmol) furnish the title compound (0.11 g, 0.29 mmol, 38%). ^{1}H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.23 (t, J = 7.0 Hz, 3H), 1.72-1.90 (m, 4H), 2.06 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.28-3.37 (m, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 6.64 (s, 1H), 6.77 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{31}N_3OS$ $(M+H)^+$: 386.3 found: 386.3.

Example 74.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.



A. (5-Bromo-4-methyl-thiophen-2-yl)-phenyl-methanol.

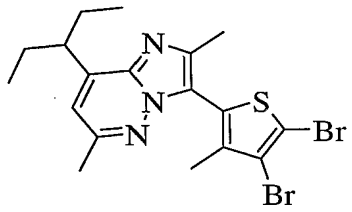
To a –78°C solution of 2-bromo-3-methyl-thiophene (4.7 g, 26.54 mmol) and Et_2O (100 mL) is added 2.0 M LDA (14.6 mL, 29.2 mmol). After 1 hour benzaldehyde (3.0 mL, 29.2 mmol) is added and the solution warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (3.29 g, 11.62 mmol, 44%). ^1H NMR ($CDCl_3$), δ 2.11 (s, 3H), 3.38-3.46 (m, 1H), 5.90 (s, 1H), 6.54 (s, 1H), 7.30-7.45 (m, 5H). LC/MS (m/z): calcd. for $C_{12}H_{11}BrOS$ $(M+H)^+$: 281.0, 283.0; found: 264.9, 266.9.

B. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanol.

Using a procedure analogous to Example 30C, from 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.1.15 mmol), (5-bromo-4-methyl-thiophen-2-yl)-phenyl-methanol (0.33 g, 1.15 mmol), 2 M Na_2CO_3 (0.86 mL, 1.72 mmol) *n*-PrOH (1 mL), $Pd(OAc)_2$ (0.0052 g, 0.023 mmol), and PPh_3 (0.018 , 0.069 mmol). The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 25-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.017 g, 0.041 mmol, 3.5%). ^1H NMR ($CDCl_3$), δ 0.86 (t, $J = 7.5$ Hz, 6H), 1.72-1.90 (m, 4H), 2.04 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 2.75 (bs, 1H), 3.26-3.38 (m, 1H), 6.05 (s, 1H), 6.65 (s, 1H), 6.76 (s, 1H), 7.30-7.45 (m, 3H), 7.50-7.56 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3OS$ $(M+H)^+$: 420.3; found: 420.3.

Example 75.

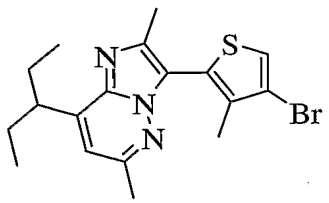
Preparation of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.00 g, 10.20 mmol) and AcOH (40 mL) is added Br_2 (0.57 mL, 11.21 mmol) and the solution heated at 110 °C overnight. Br_2 (0.57 mL, 11.21 mmol) is added and the solution heated at 110 °C for 2 hours. The solution is poured into 5 M NaOH (200 mL) and ice (200 mL). The slurry is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with water (200 mL), 20% $NaHSO_3$ (200 mL), sat. $NaHCO_3$ (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (5%-15% EtOAc gradient) furnish the title compound (2.66 g, 5.64 mmol, 55%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.12 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.25-3.35 (m, 1H), 6.69 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{21}Br_2N_3S$ $(M+H)^+$: 470.0; found: 470.3.

Example 76.

Preparation of 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

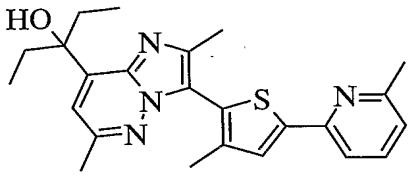


To a –78 °C solution of 3-(4,5-dibromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 g, 0.47 mmol) and THF (3 mL) is added 1.6 M *n*-BuLi (0.31 mL, 0.49 mmol). After 20 minutes the solution is quenched with water (1 mL), warmed to ambient temperature, diluted with EtOAc (30 mL), washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified

by ISCO (5%-10% EtOAc gradient) furnish the title compound (0.056 g, 0.14 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.09 (s, 3H), 2.44 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.68 (s, 1H), 7.44 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.3.

Example 77.

Preparation of 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.



A. 2-(5-Bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine.

To a –78°C solution of 2-bromo-3-methyl-thiophene (2.0 mL, 17.75 mmol) and THF (30 mL) is added 2.0 M LDA (9.76 mL, 19.52 mmol). After 45 minutes 0.5 M $ZnCl_2$ (39.0 mL, 19.50 mmol) is added and the solution stirred for 30 minutes. 2-Bromo-6-methyl-pyridine (2.4 mL, 21.29 mmol) and $Pd(PPh_3)_4$ (0.50 g, 0.44 mmol) is added and the solution is warmed to ambient temperature and stirred for 2 hour. The solution is washed with sat. NH_4Cl (20 mL). The aqueous layer is extracted with CH_2Cl_2 (30 mL). The combined organic layers are washed with sat. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (2.34 g, 8.73 mmol, 49%). ^{1}H NMR ($CDCl_3$), δ 2.21 (s, 3H), 2.54 (s, 3H), 6.99 (d, J = 7.9 Hz, 1H), 7.23 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{11}H_{10}BrNS$ $(M+H)^+$: 267.0, 269.0; found:267.7, 269.5.

B. 2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.50 g, 3.39 mmol), 2-(5-bromo-4-methyl-thiophen-2-yl)-6-methyl-pyridine (1.00 g, 3.73 mmol), Cs_2CO_3 (2.32 g, 7.13 mmol) and DMF (5 mL) is de-gassed for 15 minutes with N_2. $Pd_2(dba)_3$ (0.15 g, 0.16 mmol) and PPh_3 (0.17 g, 0.65 mmol) is added and the solution is heated at 130°C overnight. The solution is diluted with CH_2Cl_2 (30 mL) washed with water (2 x 25 mL), brine (25 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (100% EtOAc), followed by recrystalization from acetonitrile / water furnish the title compound (0.45 g, 1.35 mmol, 39%). ^{1}H NMR ($CDCl_3$), δ 2.13 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 2.57 (s, 3H), 6.90 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 8.0, 7.5 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{19}H_{18}N_4S$ $(M+H)^+$: 335.1; found: 335.1.

C. 1-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one.

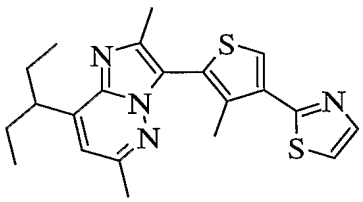
To a –78°C solution of 2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.34 g, 1.02 mmol) and THF (9 mL) is added 2.0 M LDA (0.61 mL, 1.22 mmol). After 3 minutes, *N*-methoxy-*N*-methyl-propionamide (Wolberg et. el. *Chem. Eur. J.*, 2001, 7, 4562) (1.17 g, 1.42 mmol) is added and the solution stirred for 20 minutes, warmed to ambient temperature and stirred for 30 minutes. The solution is diluted with EtOAc (50 mL) washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.10 g, 0.26 mmol, 25%). ^{1}H NMR ($CDCl_3$), δ 1.28 (t, J = 7.0 Hz, 3H), 2.13 (s, 3H), 2.54 (s, 3H), 2.58 (s, 6H), 3.59 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.55 (bs, 1H), 7.58 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{22}N_4OS$ $(M+H)^+$: 391.2; found: 391.2.

D. 3-{2,6-Dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol.

To a –0°C solution of 1-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-propan-1-one (0.040 g, 0.10 mmol) and Et_2O (5 mL) is added 3.0 M ethyl magnesium bromide (0.68 mL, 2.05 mmol). The solution is warmed to ambient temperature, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.016 g, 0.038 mmol, 37%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.92-2.01 (m, 4H), 2.14 (s, 3H), 2.46 (s, 3H), 2.53 (s, 3H), 3.57 (s, 3H), 6.39 (s, 1H), 6.66 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.57 (dd, J = 7.9, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.3; found: 421.3.

Example 78.

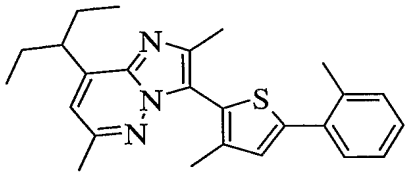
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-thiazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (3.82 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) furnish the title compound (0.19 g, 0.48 mmol, 76%). ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.36 (s, 3H), 2.47 (s, 3H), 2.50 (, 3H), 3.29-3.39 (m, 1H), 6.69 (s, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.89 (d, J = 3.3 Hz, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.2; found: 397.3.

Example 79.

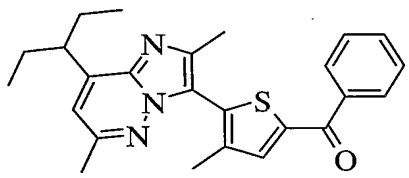
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-o-tolyl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 32, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.38 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) and 0.5M solution of 2-methylphenylzinc iodide in THF (3 mL, 1.53 mmol) furnish the title compound (0.069 g, 0.17 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.19 (s, 3H), 2.53 (s, 3H), 2.54 (s, 3H), 2.55 (s, 3H), 3.32-3.40 (m, 1H), 6.68 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 3H), 7.48-7.53 (m, 1H). LC/MS (m/z): calcd. for $C_{25}H_{29}N_3S$ $(M+H)^+$: 404.3; found: 404.3.

Example 80.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-2-yl}-phenyl-methanone.

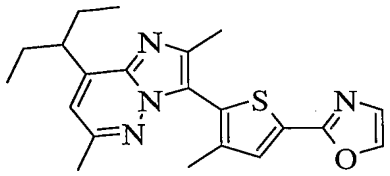


To a -78°C solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and THF (5 mL) is added 1.30 M *n*-Bu-Li (0.50 mL, 0.80 mmol). After 30 minutes *N*-methoxy-*N*-methyl-benzamide (0.13 mL, 0.84 mmol) is added, the solution is warmed to ambient temperature, and stirred overnight. The solution is diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 0.16 mmol, 21%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 6H), 1.74-1.93 (m, 4H), 2.18 (s, 3H), 2.52 (s, 3H), 2.54 (s,

3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.49-7.54 (m, 2H), 7.56 (s, 1H), 7.57-7.62 (m, 1H), 7.89-7.94 (m, 2H). LC/MS (m/z): calcd. for $C_{25}H_{27}N_3OS$ $(M+H)^+$: 418.2; found: 418.2.

Example 81.

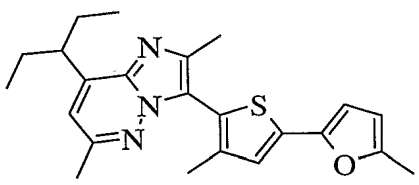
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-oxazol-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of oxazole (0.14 g, 2.04 mmol) and THF (3 mL) is added 1.6 M *t*-Bu-Li in hexane (1.32 mL, 2.14 mmol). The mixture is stirred at –78°C for 15 minutes. 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-Bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65 °C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (20 mL), water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 20-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) to furnish the title compound (0.020 g, 0.053 mmol, 5%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.49 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.69 (s, 1H), 7.19 (s, 1H), 7.59 (s, 1H), 7.65 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS$ $(M+H)^+$: 381.3; found: 381.1.

Example 82.

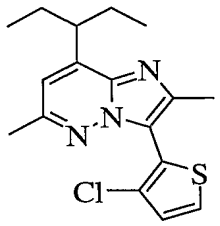
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(5-methyl-furan-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a 0°C mixture of 2-methylfuran (0.18 mL, 2.04 mmol) and Et_2O (2 mL) is added 1.6 M *t*-Bu-Li in hexane (1.30 mL, 2.14 mmol). The mixture is heated at a reflux for 30 minutes, cooled to 0°C, and 0.5 M $ZnCl_2$ in THF (4.3 mL, 2.14 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) is added and mixture is stirred at 65°C overnight, diluted with EtOAc (30 mL), washed with 10% citric acid (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20% EtOAc/hexane gradient) furnish the title compound (0.20 g, 0.51 mmol, 50%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.62 (dd, J = 3.1, 0.9 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.66 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{27}N_3OS$ $(M+H)^+$: 394.3; found: 394.2.

Example 83.

Preparation of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

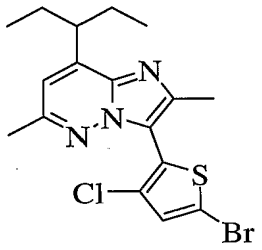


To a flask of 2-bromo-3-chloro-thiophene (Lemaire et. el., *Synth. Commun.*, 1994, 24, 95) (2.53 g, 12.82 mmol) is added 0.05 g/mL Reike® zinc in THF (25 mL, 19.24 mmol). The solution is heated at a reflux for 2 hours. The excess zinc is allowed to settle and the solution transferred to a flask containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example KW1-A03735-193) (2.01 g, 6.41 mmol) and $PdCl_2$(dppf) (0.23 g, 0.32 mmol). The solution is heated at a reflux overnight, quenched with sat. NH_4Cl (25 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (2%-15% EtOAc/hexane gradient) furnish the title compound (1.32 g, 6.68 mmol, 62%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m,

4H), 2.48 (s, 3H), 2.49 (s, 3H), 3.37-3.36 (m, 1H), 6.67 (s, 1H), 7.07 (d, J = 5.4 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H). LC/MS (m/z): calcd. for $C_{17}H_{20}ClN_3S$ $(M+H)^+$: 334.1; found: 334.1.

Example 84.

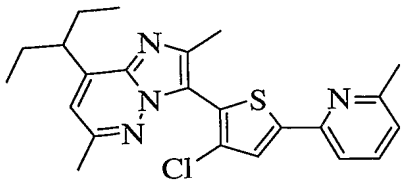
Preparation of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine. (1.15 g, 3.44 mmol) and CH_2Cl_2 (12 mL) is added NBS (0.64 g, 3.62 mmol). The solution is stirred at ambient temperature overnight, washed with water (2 x 75 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to furnish the title compound (1.36 g, 3.29 mmol, 96%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.49 (s, 3H), 2.53 (s, 3H), 3.26-3.36 (m, 1H), 6.70 (s, 1H), 7.07 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.1; found: 412.0.

Example 85.

Preparation of 3-[3-chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a flask of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (2.9 mL, 1.45

mmol). The mixture is stirred at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4CL (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) furnish the title compound (0.072 g, 0.17 mmol, 23%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.58 (s, 3H), 3.30-3.39 (m, 1H), 6.70 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.60 (dd, J = 7.7, 7.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{25}ClN_4S$ $(M+H)^+$: 425.2; found: 425.2.

Method B.

A. 2-(4-Chloro-thiophen-2-yl)-6-methyl-pyridine.

To a solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.50 g, 7.60 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (23.00 mL, 11.39 mmol) is added $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). The solution is heated at 40°C overnight, diluted with Et_2O (50 mL), washed with sat. NH_4Cl (40 mL), dried over $MgSO_4$, filtered on concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (0.45 g, 2.15 mmol, 28%). ^1H NMR ($CDCl_3$), δ 2.56 (s, 3H), 7.02 (d, 7.7 Hz, 1H), 7.13 (d, J = 0.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.54 (dd, J = 7.9, 7.7, 1H).

B. 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine.

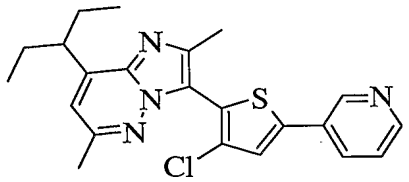
To a 0°C solution of 2-(4-chloro-thiophen-2-yl)-6-methyl-pyridine (example Rupp-96) (0.45 g, 1.45 mmol) and CH_2Cl_2 (10 mL) is added Br_2 (0.15 mL, 2.91 mmol). The solution is warmed to ambient temperature and stirred for 1 hour. The solution is washed with sat. $NaHCO_3$ (10 mL), sat. $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.59 g, 2.04, 95%). ^1H NMR ($CDCl_3$), δ 2.55 (s, 3H), 7.05 (d, 7.9 Hz, 1H), 7.29 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.9, 7.9, 1H). LC/MS (m/z): calcd. for $C_{10}H_7BrClNS$ $(M+H)^+$: 288.0; found: 287.9.

C. 3-[3-Chloro-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.39 g, 1.78 mmol), 2-(5-bromo-4-chloro-thiophen-2-yl)-6-methyl-pyridine (0.59 g, 2.04 mmol), Cs_2CO_3 (1.23 g, 3.77 mmol), and DMF (5 mL), is de-gassed with N_2 for 15 minutes. PPh_3 (0.089 g, 0.34 mmol) and $Pd_2(dba)_3$ (0.079 g, 0.86 mmol) is added and the solution heated at 110°C for 48 hours. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) and is chromatographed (19 x 300 C18 Symmetry column, 20-45% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.078 g, 0.18 mmol, 10%). Spectrum identical to Method A.

Example 86.

Preparation of 3-(3-chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

A solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), pyridine-3-boronic acid (0.082 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol) and, *n*-PrOH (1 mL), is degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.0012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added and the solution is heated at 88°C overnight. The solution is diluted with EtOAc (15 mL), washed with water (10 mL), sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO column chromatography (15-40% EtOAc/hexane gradient) furnish the title compound (0.095 g, 0.23 mmol, 38%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.71 (s, 1H), 7.32-7.37 (m, 2H), 7.85-7.90 (m, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.89 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.2; found: 411.2.

Method B.

A. 3-(4-Chloro-thiophen-2-yl)-pyridine.

A solution of 2-bromo-4-chloro-thiophene (Gronowitz, Rosén *Chemica Scripta*, 1971, 1, 33) (1.45 g, 7.34 mmol), pyridine-3-boronic acid (0.95 g, 7.71 mmol), 2 M Na_2CO_3 (5.50 mL, 11.01 mmol) and, *n*-PrOH (3 mL), is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.033 g, 0.15 mmol) and PPh_3 (0.12 g, 0.44 mmol) are added and the solution is heated at 85°C for 48 hours, diluted with CH_2Cl_2 (50 mL), washed with 10 % Na_2CO_3 (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.74 g, 3.78 mmol, 51%). ^{1}H NMR ($CDCl_3$), δ 7.12-7.13 (m, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.78-7.82 (m, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.82 (d, J = 2.2 Hz, 1H).

B. 3-(5-Bromo-4-chloro-thiophen-2-yl)-pyridine.

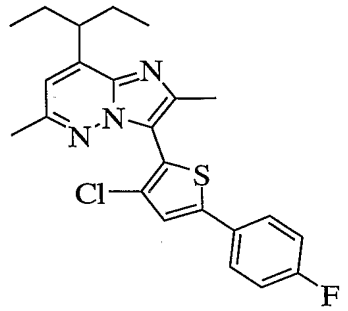
Using a procedure similar to Example 85 Method B. step B, 3-(4-chloro-thiophen-2-yl)-pyridine (0.74 g, 3.78 mmol), and Br_2 (0.39 mL, 7.56 mmol) furnish the title compound (0.99 g, 3.61 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 7.13 (s, 1H), 7.34 (dd, J = 8.1, 4.4 Hz, 1H), 7.74-7.78 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H).

C. 3-(3-Chloro-5-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure similar to Example 85 Method B Step C, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.50 g, 2.30 mmol), 3-(5-bromo-4-chloro-thiophen-2-yl)-pyridine) (0.76 g, 2.76 mmol), Cs_2CO_3 (1.57 g, 4.83 mmol), PPh_3 (0.11 g, 0.44 mmol) and $Pd_2(dba)_3$ (0.10 g, 0.11 mmol). The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.35 g, 0.85 mmol, 37%). Spectrum identical to Method A.

Example 87.

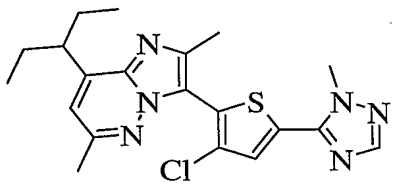
Preparation of 3-[3-chloro-5-(4-fluoro-phenyl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 25, 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-flourophenylboronic acid (0.093 g, 0.67 mmol), 2 M Na_2CO_3 (0.45 mL, 0.91 mmol), *n*-PrOH (2 mL), $Pd(OAc)_2$ (0.0068 g, 0.030 mmol) and PPh_3 (0.016 g, 0.061 mmol) furnish the title compound (0.041 g, 0.096 mmol, 16%). ^1H NMR ($CDCl_3$), δ 0.89 (t, $J = 7.5$ Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.07-7.13 (m, 2H), 7.22 (s, 1H), 7.54-7.60 (m, 2H). LC/MS (m/z): calcd. for $C_{23}H_{23}ClFN_3S$ $(M+H)^+$: 428.2; found: 428.1.

Example 88.

Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Method A.

To a –78 °C solution of 1-methyl-1,2,4-triazole (0.18 mL, 2.33 mmol) and THF (3 mL) is added a 1.56 M solution of *n*-Bu-Li in hexanes (1.49 mL, 2.33 mmol). The solution is stirred at –78°C for 30 minutes, 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature. 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g,

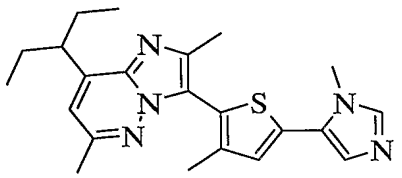
0.78 mmol) and $PdCl_2$(dppf) (0.028 g, 0.039 mmol) is added and the solution heated at 60 °C for 2 days, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-10% EtOAc/hexane gradient) furnish the title compound (0.19 g, 0.46 mmol, 59%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.76-1.94 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.29-3.37 (m, 1H), 4.16 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.1.

Method B.

A 5-L reaction flask equipped with a cooling bath, air stirrer, gas dispersion tube and thermometer probe is charged with 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-1H-[1,2,4]triazole (162.0 g, 0.745 moles), 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (250.1 g, 0.898 moles), NMP (800 mL), KOAc (366.0 g), TBABr (50.5 g), and additional NMP (700 mL) to form a mixture. While stirring, N_2 is bubbled through the mixture for 1 hour. A mixture of $Pd(OAc)_2$ (8.37 g) and TDBPP (24.56 g) are added in one portion, then heated to 120 °C for 3 hours. The reaction is cooled to 50 °C and transferred to a 12 L flask. The mixture is cooled to 20-25 °C, then added de-ionized H_2O (3.5 L) is added dropwise to precipitate out a sticky solid that gradually solidifies with stirring overnight. The solids are filtered, washed with de-ionized H_2O (2 x 2L), and fried on the filter plate for 30-60 minutes. The crude solids (595 g) are warmed in EtOAc (6.0 L) to 30 °C, then filtered through GFF paper to remove insolubles. The filtrate is dried over Na_2SO_4, treated with Darco (30.0 g), heated to 35 °C, filtered, and concentrated to give brown solids (432 g). The crude solids are eluted through a silica plug (1.0 kg) with CH_2Cl_2 (4.0 L), followed by EtOAc (16.0 L). Similar fractions are combined and concentrated under vacuum to approximately 6.0 L, then treated with Darco overnight with stirring. After filtering off the Darco through GFF paper, the filtrate is concentrated to solids (336 g). The solids are crystallized from EtOAc: heptane (1:2) to afford the title compound as a pale yellow solid (187 g, 60.5%, >98% area-% by reverse phase: Zorbax SB-C8, 4.6 mm x 250 mm, 5 microns, UV = 218 nm, flow rate 1.0 mL/min., oven temp. 25°C, isocratic = 30% water (0.1% TFA) & 70% AcCN.

Example 89.

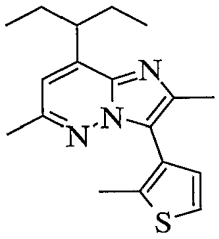
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(3-methyl-*3H*-imidazol-4-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 31, 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34M *n*-Bu-Li (0.80 mL, 1.07 mmol), 0.5M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 5-iodo-1-methyl-*1H*-imidazole (0.24 g, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.061g, 0.15 mmol, 15%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.17 (s, 3H), 2.50 (s, 3H), 2.53 (s, 3H), 3.24-3.38 (m, 1H), 3.61 (s, 3H), 6.68 (s, 1H), 7.02 (s, 1H), 7.23 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.3; found: 394.2.

Example 90.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 4,4,5,5-Tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane.

A mixture of 3-bromo-2-methyl-thiophene (Saika et. el. *Chem. Soc. Chem. Communication*, 18, 1994, 2133; Steinkopf et. el.; *Justus Liebigs Ann. Chem.*, 513, 1934, 281; 3.1 g, 17.51 mmol), DMSO (50 mL), 4,4,5,5,4',4',5',5'-Octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (4.90g, 19.26 mmol), and KOAc (5.20 g, 52.58 mmol) is de-gassed with N_2 for 15 minutes. $PdCl_2$(dppf) (0.70 g, 0.88 mmol) is added and the solution stirred at ambient temperature overnight, then warmed to 85°C for 3 hours. The solution is diluted with water (200 mL), extracted with EtOAc (2 x 100 mL). The

combined organic layers washed with water (2 x 200 mL), brine (200 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (5%-20% EtOAc/hexane gradient) furnish the title compound (1.52 g, 6.78 mmol, 39%). ^1H NMR ($CDCl_3$), δ 1.34 (s, 12H), 2.72 (s, 3H), 7.04 (d, J = 5.0 Hz, 1H), 7.22 (d, 5.0 Hz, 1H).

B. 2-Methyl-thiophene-3-boronic acid.

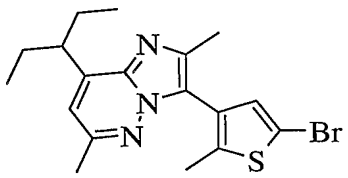
To a solution of 4,4,5,5-tetramethyl-2-(2-methyl-thiophen-3-yl)-[1,3,2]dioxaborolane (1.52 g, 6.78 mmol), acetone (15 mL) and water (15 mL) is added $NaIO_4$ (2.90 g, 13.56 mmol). The solution is stirred at ambient temperature for 24 hours, then heated to a reflux for 24 hours. The solution is concentrated dissolved in EtOAc (1450 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.75g, 5.49 mmol, 78%). ^1H NMR ($CDCl_3$), δ 2.93 (s, 3H), 7.10 (d, J = 5.3 Hz, 1H), 7.51 (d, 5.3 Hz, 1H).

C. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

(1.65 g, 4.80 mmol), 2-methyl-thiophene-3-boronic acid (0.75 g, 5.28 mmol), 2 M Na_2CO_3 (3.60 mL, 7.20 mmol) and *n*-PrOH (20 mL) is degassed with N_2 for 10 minutes. $Pd(OAc)_2$ (0.022 g, 0.096 mmol) PPh_3 (0.076 g, 0.29 mmol) is added and the solution heated at 60°C for 24 hours, then heated at 90°C for 24 hours. The solution is concentrated, diluted in EtOAc (50 mL) washed with 10% Na_2CO_3 (40 mL), water (40 mL), brine (40 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-15% EtOAc/hexane gradient) furnish the title compound (0.78 g, 2.49 mmol, 52%). ^1H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.74-1.94 (m, 4H), 2.38 (s, 3H), 2.44 (s, 3H), 2.50 (s, 3H), 3.30-3.40 (m, 1H), 6.64 (s, 1H), 7.11 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3S$ $(M+H)^+$: 314.2; found: 314.2.

Example 91.

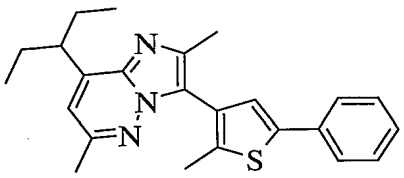
Preparation of 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine. (0.76 g, 2.42 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.60 g, 3.37 mmol). The solution is stirred at ambient temperature for 2 hours and concentrated. The solution is dissolved in Et_2O (30 mL) washed with water (3 x 30 mL), brine (30 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.95 g, 2.42 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.31 (s, 3H), 2.42 (s, 3H), 2.51 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3S$ $(M+H)^+$: 392.2; found: 392.1.

Example 92.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-phenyl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.

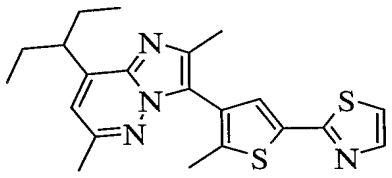


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) and 0.5 M solution of phenylzinc iodide in THF (2.0 mL, 1.02 mmol). The residue is purified by column chromatography (0-10% EtOAc/hexane gradient) and is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient) furnish the title compound (0.081 g, 0.21 mmol, 41%). ^{1}H NMR ($CDCl_3$), δ 0.90 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.40 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.32-3.41 (m, 1H), 6.66 (s, 1H), 7.23-7.30 (m, 1H),

7.32 (s, 1H), 7.34-7.41 (m, 2H), 7.57-7.63 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{27}N_3S$ $(M+H)^+$: 390.2; found: 390.2.

Example 93.

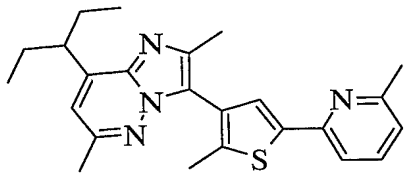
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-thiophen-3-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 0.5 M 2-thiazolylzinc bromide in THF (8.1 mL, 4.05 mmol) and $PdCl_2$(dppf) (0.019 g, 0.025 mmol) furnish the title compound (0.20 g, 0.50 mmol, >99%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.40 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.60 (s, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.52 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4S_2$ $(M+H)^+$: 397.1; found: 397.2.

Example 94.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[2-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-3-yl]-imidazo[*1,2-b*]pyridazine.

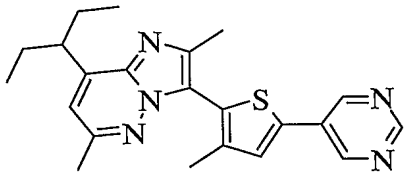


Using a procedure similar to Example 32, from 3-(5-bromo-2-methyl-thiophen-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.24 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.031 mmol) and 0.5 M solution of 6-methyl-2-pyridylzinc bromide in THF (3.7 mL, 1.84 mmol) furnish the title compound (0.086 g, 0.21 mmol, 34%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.39 (s, 3H), 2.46 (s, 3H), 2.51 (s, 3H), 2.57 (s, 3H), 3.31-3.40 (m, 1H), 6.65 (s, 1H), 6.97 (d, J = 7.8 Hz,

1H), 7.41 (d, J = 7.8 Hz, 1H), 7.50-7.56 (m, 2H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4$ $(M+H)^+$: 405.2; found: 405.2.

Example 95.

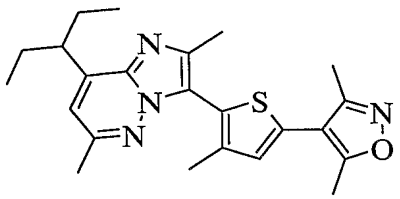
Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-5-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 74B, from of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.51 mmol), 5-pyrimidine boronic acid (0.076 g, 0.61 mmol), 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), $Pd(OAc)_2$ (0.0023 g, 0.011 mmol), PPh_3 (0.0080 g, 0.0031 mmol), and *n*-PrOH (2 mL) is furnished the title compound (0.084 g, 0.21 mmol, 42%). ^1H NMR ($CDCl_3$), δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.91 (m, 4H), 2.17 (s, 3H), 2.48 (s, 3H), 2.51 (s, 3H), 3.26-3.36 (m, 1H), 6.69 (s, 1H), 7.74 (s, 1H), 8.95 (s, 2H), 9.10 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 96.

Preparation of 3-[5-(3,5-Dimethyl-isoxazol-4-yl)-3-methyl-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

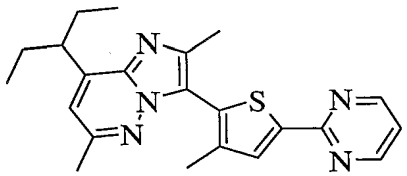


To a flask of 4-iodo-3,5-dimethyl-isoxazole (0.34 g, 1.53 mmol) is added a solution of Rieke® zinc 5g/100 mL in THF (3 mL, 2.29 mmol). The slurry is heated at a reflux for 4 hours, the zinc is allowed to settle and the solution transferred to a flask of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol) and $PdCl_2$(dppf) (0.028 g, 0.038 mmol). The solution is

heated at 50 °C overnight, diluted with EtOAc (20 mL), washed with 0.1 M HCl (15 mL), water (15 mL), brine (15 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.22 g, 0.54 mmol, 71%). ^{1}H NMR ($CDCl_3$), δ 0.92 (t, J = 7.5 Hz, 6H), 1.78-1.96 (m, 4H), 2.21 (s, 3H), 2.47 (s, 3H), 2.53 (s, 3H), 2.56 (s, 3H), 2.61 (s, 3H), 3.33-3.42 (m, 1H), 6.72 (s, 1H), 6.98 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}N_4OS$ $(M+H)^+$: 409.3; found: 409.2.

Example 97.

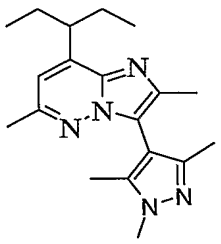
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyrimidin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



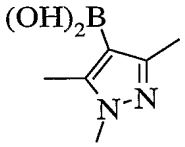
A solution of 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.76 mmol), 2-tributylstannanyl-pyrimidine (0.34 g, 0.92 mmol) and THF (5 mL) is de-gassed with N_2 for 10 minutes Triphenylarsine (0.047 g, 0.15 mmol) and $Pd_2(dba)_3$ (0.035 g, 0.038 mmol) is added and the solution heated at 55°C for 48 hours and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient), dissolved in acetonitrile (20 mL), washed with hexane (3 x 20 mL) and concentrated to furnished the title compound (0.097 g, 0.25 mmol, 32%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.4 Hz, 6H), 1.74-1.92 (m, 4H), 2.18 (s, 3H), 2.51 (s, 3H), 2.52 (s, 3H), 3.29-3.38 (m, 1H), 6.67 (s, 1H), 7.08 (t, J = 4.8, 1H), 7.93 (s, 1H), 8.69 (s, 2H). LC/MS (m/z): calcd. for $C_{22}H_{25}N_5S$ $(M+H)^+$: 392.3; found: 392.2.

Example 98.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



A. 1,3,5-Trimethylpyrazole-4-boronic acid.



To a dry flask is added 300 mg (1.59 mmol) of 4-bromo-1,3,5-trimethyl pyrazole to 4.0 ml THF. The mixture is cooled to -78^0C and 1eq of n-BuLi (1.6 M) is added via syringe. The mixture is stirred 1.5 hrs, and 0.19ml of trimethylborate (1.08 eq) is added. The reaction mixture is stirred 2 hrs, allowing bath to reach -10^0C, then 1.5 ml of 5N HCl is added and stirred 30 minutes longer. The aqueous layer is extracted 3 times with ethyl acetate. The combined organics are dried over MgSO4, filtered, and evaporated to an oil. The oil is dissolved in methanol/methylene chloride and re-evaporated. The residue is triturated with acetone/ethyl acetate then filtered to obtain title compound as a white solid 92.1 mg (37.6%). ^{1}H-NMR (DMSO-d_6): δ5.92 (s); 3.72 (s, 3H); 2.34 (s, 3H); 2.26 (s, 3H) ppm.

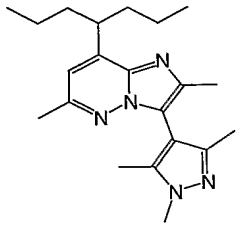
B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.

3-Iodo-2,6-dimethyl-8-(1-ethyl-propyl)-imidazo[*1,2-b*]pyridazine (200mg, 0.582 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (233mg, 1.53 mmol), Pd(PPh3)4 (13.4mg, 0.01 mmol) are combined in a microwave pressure tube. Then 0.58 ml of 2N Na2CO3 and 3.0ml of dimethoxyethane/H20/ethanol (7:3:2) solution is added. The mixture is microwaved at 155^0C for 20minutes. Water is added and the mixture is extracted four times with ethyl acetate. The combined organics are dried over MgSO4, filtered, then

evaporated to a residue which is chromatographed using hexanes, then 1:1 hexanes: ethyl acetate, then 100% ethyl acetate to give the title compound (6.4%) as a yellow oil. ^{1}H-NMR (DMSO-d_6): δ6.86 (s, 1H); 3.73 (s, 3H); 3.06-3.10 (m, 1H); 2.41 (s, 3H); 2.22 (s, 3H); 2.03 (s, 3H); 1.93 (s, 3H); 1.74-1.83 (m, 4H); 0.77 (t, J = 7.26 Hz, 6H) ppm. MS/ ES+ = 327 (100%, M+2).

Example 99.

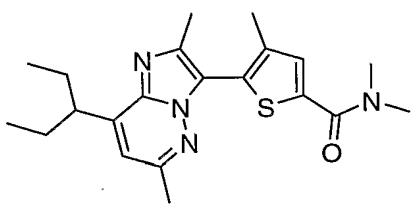
Preparation of 2,6-Dimethyl-8-(1-propyl-butyl)-3-(1,3,5-trimethyl-*1H*-pyrazol-4-yl)-imidazo[*1,2-b*]pyridazine.



3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (75 mg, 0.20 mmol), 1,3,5-trimethylpyrazole-4-boronic acid (80 mg, 0.52 mmol), 2N Na2CO3 solution (0.22 ml), and 5.0mg (0.0004 mmol) of Pd(PPh3)4 are combined in microwave pressure vessel with 1.5ml of dimethylether/H2O/ethanol (7:3:2) solution. The mixture is microwaved at 140^{0}C for 25 minutes. The mixture is evaporated and chromatographed on silica gel column using hexanes then 3:1 hexane:ethyl acetate, then 1:1 hexane:ethyl acetate to give the title compound (22.8%) as a clear oil. ^{1}H-NMR (DMSO-d_6): δ6.88 (s, 1H); 3.72 (s, 3H); 3.06-3.10 (m, 1H); 2.40 (s, 3H); 2.21 (s, 3H); 2.02 (s, 3H); 1.92 (s, 3H); 1.60-1.76 (m, 4H); 1.08-1.21 (m, 4H); 0.82 (t, J = 7.49 Hz, 6H) ppm. MS/ ES+ = 354 (100%, M+1).

Example 100.

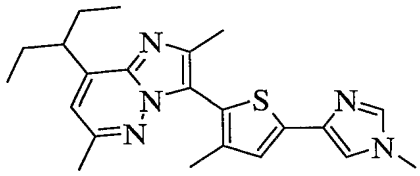
Preparation of 5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid dimethylamide.



Using a procedure analogous to Example 23 B, 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophene-2-carboxylic acid (151 mg, 0.42 mmol) and 2.0 M dimethylamine (2.0 mL, 4 mmol) give the title compound (161 mg, 0.42 mmol, 100%). 1H NMR (CDCl3): δ 0.89 (t, J = 7.4 Hz, 6H), 1.75-1.94 (m, 4H), 2.14 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.15-3.50 (m, 7H), 6.72 (s, 1H), 7.30 (s, 1H). ES-MS (m/z): calcd for C21H28N4OS (M+H)+: 385.6 found: 385.3.

Example 101.

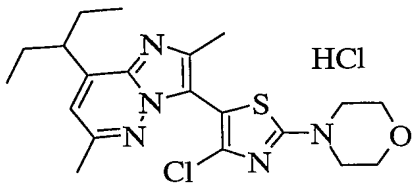
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(1-methyl-*1H*-Imidazol-3-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 31. from 3-(5-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 1.02 mmol), 1.34 M *n*-BuLi (0.80 mL, 1.07 mmol), 0.5 M $ZnCl_2$ in THF (2.14 mL, 1.07 mmol), 3-iodo-1-methyl-*1H*-imidazole (0.24 mL, 1.22 mmol) and $PdCl_2$(dppf) (0.037 g, 0.051 mmol) furnish the title compound (0.030g, 0.076 mmol, 8%). ^{1}H NMR ($CDCl_3$), δ 0.89 (t, *J* = 7.5 Hz, 6H), 1.74-1.93 (m, 4H), 2.13 (s, 3H), 2.50 (s, 3H), 2.51 (s, 3H), 3.31-3.40 (m, 1H), 3.72 (s, 3H), 6.66 (s, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 7.19 (s, 1H), 7.86 (d, *J* = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}N_5S$ $(M+H)^+$: 394.2; found: 394.2.

Example 102.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine, hydrochloride salt.

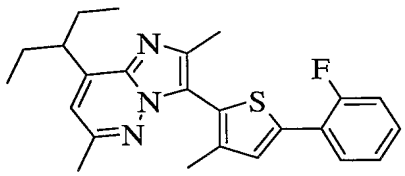


IPA (225.0 mL) is added to compound N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (18.8 g, 0.0448 mmol,

below) in a 1 L 1-neck round-bottomed flask The starting material slurry is heated to 50 °C on a Buchi bath, at which time a hazy solution resulted. Concentrated (12 M) aqueous HCl (3.73 mL, 0.0448 mmole, 1.0 eq) is added all at once, and the hazy solution is stirred at 50 °C on the Buchi for 10 minutes, then evaporated to a yellow solid under vacuum. After 20 minutes at room temperature under vacuum (weight of 20.9 g), acetone (100 mL) is added and the resulting yellow slurry is stirred at room temperature for 1 hour, then cooled with an ice bath and stirred for an additional 1 hour. The slurry is filtered, rinsed with acetone, and dried overnight under vacuum at 40°C to provide pale yellow-white crystalline solid 19.18 g (94%). ^{1}H NMR (DMSO): δ 7.52 (s, 1H), 3.73 (t, J = 4.6, 4H), 3.49 (t, J = 5.2 Hz, 4H), 3.39 (m, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 1.77 (m, 4H), 0.80 (t, J = 7.4 Hz, 6H).

Example 103.

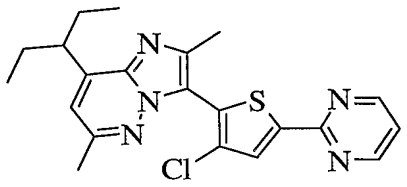
Preparation of 8-(1-ethyl-propyl)-3-[5-(2-fluoro-phenyl)-3-methyl-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 30 B, 3-(5-boronic acid-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.18 g, 0.50 mmol), 1-bromo-2-fluoro-benzene (0.072 g, 0.65 mmol), and 2 M Na_2CO_3 (0.38 mL, 0.76 mmol), *n*-PrOH (2 mL), and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) furnish the title compound (0.022 g, 0.054 mmol, 11%). ^{1}H NMR ($CDCl_3$), δ 0.93 (t, *J* = 7.4 Hz, 6H), 1.71-1.96 (m, 4H), 2.19 (s, 3H), 2.66 (s, 3H), 2.67 (s, 3H), 3.41-3.50 (m, 1H), 7.15 (s, 1H), 7.15-7.23 (m, 2H), 7.28-7.35 (m, 1H), 7.45 (d, *J* = 1.4 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{26}FN_3S$ $(M+H)^+$: 408.2; found: 408.2.

Example 104.

Preparation of 3-(3-chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 5.97 mmol) and THF (30 mL) is added 1.6 M *n*-BuLi (4.1 mL). After 30 minutes $B(OMe)_3$ (0.74 mL, 6.59 mmol) is added, the solution is warmed to ambient temperature and stirred overnight. 1 M HCl (30 mL) is added and the solution stirred for 20 minutes. The solution is made basic with 5 M NaOH. The organic layer is extracted with 1 M NaOH (30 mL). The combined aqueous layers are made acidic with 5 M HCl, K_3PO_4•3 H_2O is added and the PH adjusted to 5.5 using 1 M NaOH. The combined aqueous layers are extracted with EtOAc (200 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (2.20 g, 5.82 mmol, 97%). LC/MS (m/z): calcd. for $C_{17}H_{21}BClN_3O_2S$ $(M+H)^+$: 378.7; found: 378.0.

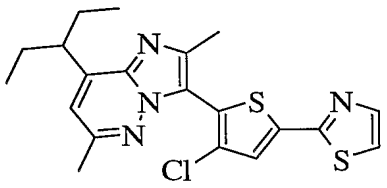
B. 3-(3-Chloro-5-pyrimidin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), and *i*-PrOH (3 mL) are degassed with N_2 for 15 minutes. $Pd(OAc)_2$ (7.4 mg, 0.033 mmol) and PPh_3 (0.026 g, 0.099 mmol) are added and the solution is heated at 90 °C overnight. The solution is diluted with EtOAc (35 mL), washed with 10% Na_2CO_3 (35 mL), brine (35 mL), dried over Na_2SO_4, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (0.077 g, 0.19 mmol, 29%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.4 Hz, 6H), 1.75-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H),

3.27-3.40 (m, 1H), 6.71 (s, 1H), 7.16 (t, J = 5.0 Hz, 1H), 8.00 (s, 1H), 8.74 (d, J = 5.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.2.

Example 105.

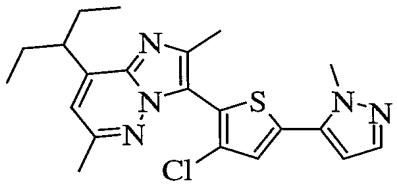
Preparation of 3-(3-chloro-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 2-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.099 g, 0.24 mmol, 35%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.71 (s, 1H), 7.33 (t, J = 3.3 Hz, 1H), 7.49 (s, 1H), 7.81 (d, J = 3.3 Hz, 2H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 417.1; found: 417.1.

Example 106.

Preparation of 3-[3-chloro-5-(2-methyl-2*H*-pyrazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

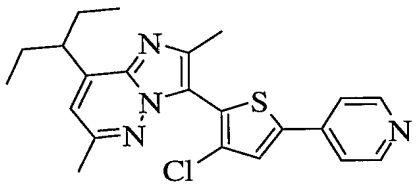


To a –78 °C solution of 1-methyl-*1H*-pyrazole (0.12 g, 1.45 mmol) and THF (4 mL) is added 1.6 M *n*-BuLi (0.91 mL, 1.45 mmol). After 45 minutes 0.5 M $ZnCl_2$ (2.9 mL, 1.45 mmol) is added and the solution is warmed to ambient temperature. After 30 minutes 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (example Rupp-88) (0.30 g, 0.73 mmol) and $PdCl_2$(dppf) (0.027

g, 0.036 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.15 g, 0.36 mmol, 50%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 6H), 3.26-3.36 (m, 1H), 4.05 (s, 3H), 6.45 (d, J = 1.9 Hz, 1H), 6.71 (s, 1H), 7.14(s, 1H), 7.49 (d, J = 1.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}ClN_5S$ $(M+H)^+$: 414.2; found: 414.2.

Example 107.

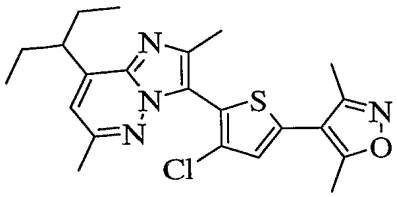
Preparation of 3-(3-chloro-5-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyridine hydrochloride (0.26 g, 1.32 mmol), 2 M Na_2CO_3 (1.00 mL, 1.99 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.16 g, 0.59 mmol, 59%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 6.72 (s, 1H), 7.45-7.49 (m, 3H), 8.63 (d, J = 1.3 Hz, 1H), 8.64 (d, J = 1.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 411.1; found: 411.1.

Example 108.

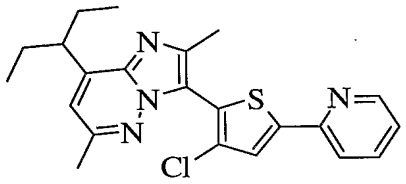
Preparation of 3-[3-chloro-5-(3,5-dimethyl-isoxazol-4-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-iodo-3,5-dimethyl-isoxazole (0.30 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol) and *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.14 g, 0.50 mmol, 50%). ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.43 (s, 3H), 2.53 (s, 6H), 2.57 (s, 3H), 3.27-3.38 (m, 1H), 6.71 (s, 1H), 7.01 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{25}ClN_4OS$ $(M+H)^+$: 429.2; found: 429.2.

Example 109.

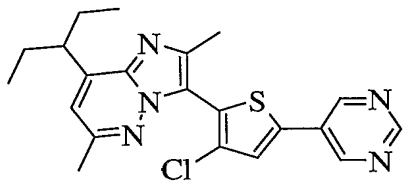
Preparation of 3-(3-chloro-5-pyridin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 g, 0.61 mmol) and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) is added a 0.5 M solution of 2-pyridylzinc bromide (2.40 mL, 1.21 mmol) and the solution heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-40% EtOAc/hexane gradient) followed by recrystallization from CH_3CN furnish the title compound (0.15 g, 0.36 mmol, 60%). ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.93 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.29-3.38 (m, 1H), 6.70 (s, 1H), 7.17-7.23 (m, 1H), 7.56 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.70-7.76 (m, 1H), 8.59 (d, J = 4.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{23}ClN_4S$ $(M+H)^+$: 412.0; found: 412.4.

Example 110.

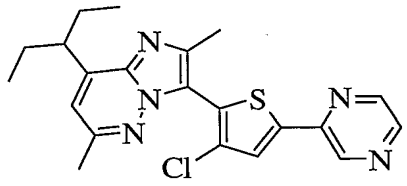
Preparation of 3-(3-chloro-5-pyrimidin-5-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25g, 0.66 mmol), 4-bromo-pyrimidine (0.21 g, 1.32 mmol), 2 M Na_2CO_3 (0.66 mL, 1.32 mmol), *i*-PrOH (3 mL), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), and PPh_3 (0.026 g, 0.099 mmol) furnish the title compound (0.053 g, 0.13 mmol, 20%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.27-3.37 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H), 8.97 (s, 2H), 9.18 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 411.2.

Example 111.

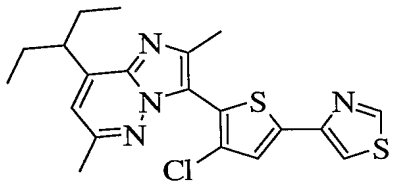
Preparation of 3-(3-chloro-5-pyrazin-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 104, 3-(3-chloro-thiophen-2-yl-5-boronic acid)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.40g, 1.06 mmol), 2-iodo-pyrazine (0.16 g, 1.59 mmol), 2 M Na_2CO_3 (1.06 mL, 2.12 mmol) and *i*-PrOH (5 mL), $Pd(OAc)_2$ (0.012 g, 0.053 mmol), and PPh_3 (0.042 g, 0.16 mmol) furnish the title compound (0.15 g, 0.36 mmol, 34%). ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.25-3.37 (m, 1H), 6.71 (s, 1H), 7.66 (s, 1H), 8.45 (d, J = 2.6 Hz, 1H), 8.51-8.53 (m, 1H), 8.96 (d, J = 1.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClN_5S$ $(M+H)^+$: 412.1; found: 412.3.

Example 112.

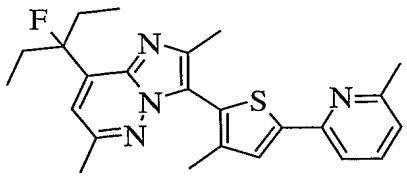
Preparation of 3-(3-chloro-5-thiazol-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a 0 °C solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.60 g, 1.45 mmol) and THF (2 mL) is added 0.05 g/mL of Reike® Zn (3.80 mL, 2.91 mmol). The solution is heated at a reflux for 1 hour, and the excess Zn allowed to settle for 1 hour at ambient temperature. The solution is transferred to a flask of 4-bromo-thiazole (Kelly, T. et al. *Tetrahedron Lett.* 1995, 51, 9293) (0.29 g, 1.74 mmol). $PdCl_2$(dppf) (0.027 g, 0.036 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (40 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) to furnish the title compound (0.098 g, 0.24 mmol, 16%). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.28-3.38 (m, 1H), 6.70 (s, 1H), 7.45 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H). LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.3.

Example 113.

Preparation of 8-(1-ethyl-1-fluoro-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.

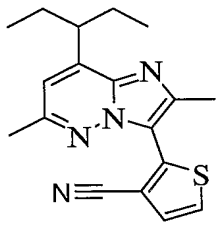


To a –78 °C solution of 3-{2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazin-8-yl}-pentan-3-ol (0.23 g, 0.55 mmol) and CH_2Cl_2 (3 mL) is added a solution of [bis(2-methoxyethyl)amino]sulfur triflouride (0.14 g, 0.60 mmol) and CH_2Cl_2 (2 mL). The solution is warmed to ambient temperature and

stirred overnight. The solution is washed with sat. $NaHCO_3$ (5 mL) and concentrated. The reside is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.13g, 0.31 mmol, 57%). ^1H NMR ($CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 6H), 2.14 (s, 3H), 2.16-2.31 (m, 2H), 2.46 (s, 3H), 2.54 (s, 3H), 2.56 (s, 3H), 2.59-2.70 (m, 2H), 6.98 (s, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{27}FN_4S$ $(M+H)^+$: 423.2; found: 423.4.

Example 114.

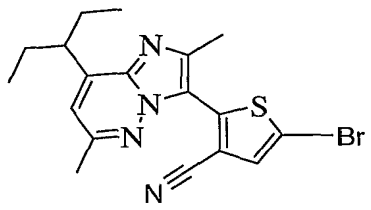
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution 0.05 g/mL of Reike® Zn (31 mL, 23.93 mmol) is added 2-bromo-thiophene-3-carbonitrile (Fournari, P. et al. Bull. Soc. Chim. Fr., 1967, 4115) (2.25 g, 11.96 mmol) and THF (5 mL). The solution is heated at a reflux for 2 hours, cooled to ambient temperature and the excess Zn allowed to settle. The solution is transferred via a cannula into a flask of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.5 g, 7.98 mmol) and $PdCl_2$(dppf) (0.29 g, 0.040 mmol). The mixture is heated at 65°C overnight, diluted with EtOAc (75 mL), washed with sat. NH_4Cl (2 x 75 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-20% EtOAc/hexane gradient) furnish the title compound (1.10 g, 3.39 mmol, 42%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.55 (s, 3H), 2.61 (s, 3H), 3.25-3.34 (m, 1H), 6.75 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.2 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{20}N_4S$ $(M+H)^+$: 325.5; found: 325.2.

Example 115.

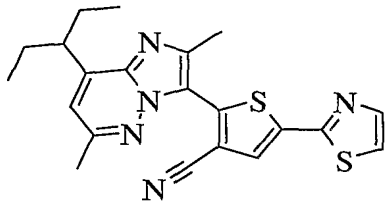
Preparation of 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile.



To a solution of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.83 g, 2.56 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.48 g, 2.69 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (1.03 g, 2.55 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.56 (s, 3 H), 2.60 (s, 3H), 3.24-3.32 (m, 1H), 6.76 (s, 1H), 7.30 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{19}BrN_4S$ $(M+H)^+$: 404.4; found: 404.1.

Example 116.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.

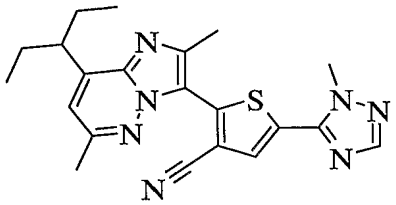


To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added a solution of 0.5 M 2-thiazolylzinc bromide (6.0 mL, 3.10 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.16 g, 0.39 mmol, 64%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3H), 2.66 (s, 3H), 3.25-3.35 (m, 1H), 6.78 (s, 1H), 7.38 (d, J = 3.5

Hz, 1H), 7.70 (s, 1H), 7.84 (d, J = 3.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{21}N_5S_2$ $(M+H)^+$: 408.6; found: 408.1.

Example 117.

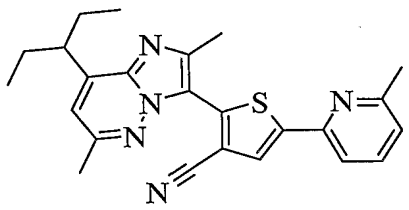
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-thiazol-2-yl-thiophene-3-carbonitrile.



To a –78 °C solution of 1-methyl-1,2,4-triazole (0.14 mL, 1.86 mmol) and THF (5 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (1.20 mL, 1.86 mmol) after 30 minutes a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (example Rupp-122) (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.023 g, 0.031 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), and is chromatographed (50 x 250 C18 X-Terra RP column, 30-90% 10 mM NH_4HCO_3/water/5 % ACN: ACN gradient). The residue is dissolved in Et_2O (25 mL), washed with sat. $NaHCO_3$ (25 mL), dried over MgSO4, filtered and concentrated to furnish the title compound (0.013 g, 0.032 mmol, 5%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.93 (m, 4H), 2.58 (s, 3 H), 2.67 (s, 3H), 3.26-3.34 (m, 1H), 4.17 (s, 3H), 6.79 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{23}N_7S$ $(M+H)^+$: 406.5; found: 406.2.

Example 118.

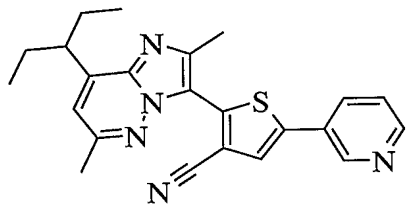
Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-(6-methyl-pyridin-2-yl)-thiophene-3-carbonitrile.



To a flask containing 5-bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.25 g, 0.62 mmol) and $PdCl_2$(dppf) (0.024 g, 0.033 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.50 mL, 1.24 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-25% EtOAc/hexane gradient), furnish the title compound (0.11 g, 0.26 mmol, 39%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.76-1.92 (m, 4H), 2.57 (s, 3 H), 2.58 (s, 3H), 2.65 (s, 3H), 3.26-3.35 (m, 1H), 6.75 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 7.9, 7.5 Hz, 1H), 7.74 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{25}N_5S$ $(M+H)^+$: 416.6; found: 416.2.

Example 119.

Preparation of 2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-5-pyridin-3-yl-thiophene-3-carbonitrile.

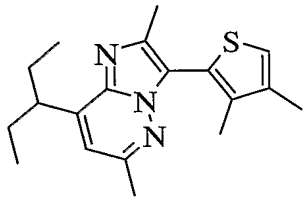


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol), 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol), and THF (2 mL) is added 1.7 M *t*-BuLi (1.85 mL, 3.15 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 5-Bromo-2-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophene-3-carbonitrile (0.21 g, 0.52 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.026 mmol) are added and the solution

heated at 55 °C for 1 hour, cooled to ambient temperature and stirred overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-40% EtOAc/hexane gradient), furnish the title compound (0.15 g, 0.37 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.58 (s, 3 H), 2.66 (s, 3H), 3.26-3.35 (m, 1H), 6.78 (s, 1H), 7.34-7.46 (m, 1H), 7.56 (s 1H), 7.91 (d, J = 7.1 Hz, 1H), 8.62 (s, 1H), 8.91 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{23}N_5S$ $(M+H)^+$: 402.6; found: 402.4.

Example 120.

Preparation of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 2-Bromo-3,4-dimethyl-thiophene.

To a solution of 3,4-dimethyl-thiophene (2.0 g, 17.82 mmol) (Minato et. al., *Tetrahedron* 1982, 38, 3347) in CH_2Cl_2 (20 mL) is added NBS (3.3 g, 18.72 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated. The residue is purified by ISCO column chromatography (100% hexane) furnish the title compound (3.0 g, 16.70 mmol). ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.17 (s, 3H), 6.85 (s, 1H).

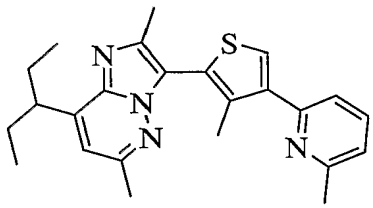
B. 3-(3,4-Dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3,4,3',4'-tetramethyl-[2,2']bithiophenyl-5-yl)-imidazo[*1,2-b*]pyridazine, respectively.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.30 g, 10.58 mmol), 2-bromo-3,4-dimethyl-thiophene (3.03 g, 15.88 mmol) and Cs_2CO_3 (7.24 g, 22.23 mmol) and DMF (50 mL) is de-gassed with N_2 for 20 minutes. $Pd_2(dba)_3$ (0.48 g, 0.053 mmol) and PPh_3 (0.56 g, 0.21 mmol) are added and the solution is heated at 120°C overnight. The solution is diluted with EtOAc (200 mL), washed with water (3 x

200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated. The residue is purified by ISCO column chromatography (10% -15% EtOAc/hexane gradient) furnish 2.04 g of a brown oil which is chromatographed (50 x 250 C18 Symmetry column, 30-70% water: 0.1 % TFA /ACN gradient) furnish the title compound (0.41 g, 1.25 mmol, 12%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.94 (m, 4H), 2.00 (s, 3 H), 2.24 (d, J = 1.0 Hz, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 3.29-3.38 (m, 1H), 6.65 (s, 1H), 7.10 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{25}N_3S$ $(M+H)^+$: 328.5; found: 328.3.

Example 121.

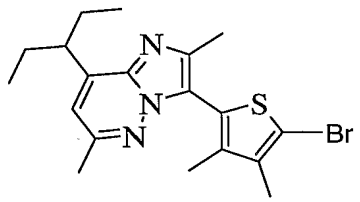
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (below) (0.25 g, 0.64 mmol) and $PdCl_2$(dppf) (0.023 g, 0.032 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (2.5 mL, 1.27 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-20% EtOAc gradient) and is chromatographed (50 x 250 C18 Symmetry column, 10-70% water: 0.1 % TFA /ACN: 0.1% TFA gradient). The residue is dissolved in Et_2O (20 mL), washed with sat. $NaHCO_3$ (15 mL) dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.20 (s, 3 H), 2.47 (s, 3H), 2.49 (s, 3H), 2.61 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.5, 7.8 Hz, 1H), 7.72 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.3.

Example 122.

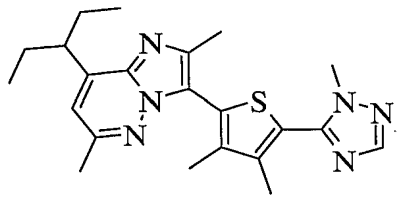
Preparation of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 3-(3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.41 g, 1.25 mmol) and CH_2Cl_2 (30 mL) is added NBS (0.23 g, 1.32 mmol). The solution is stirred for 1 hour, diluted with Et_2O (100 mL), washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) filtered and concentrated to furnish the title compound (0.41 g, 1.01 mmol, 80%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.4 Hz, 6H), 1.72-1.94 (m, 4H), 2.02 (s, 3 H), 2.18 (s, 3H), 2.43 (s, 3H), 2.49 (s, 3H), 3.27-3.36 (m, 1H), 6.67 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{24}BrN_3S$ $(M+H)^+$: 407.4; found: 407.3.

Example 123.

Preparation of 3-[3,4-dimethyl-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

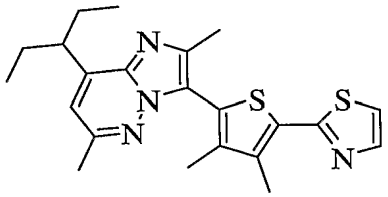


To a –78 °C solution of 1-methyl-1,2,4-triazole (0.056 mL, 0.74 mmol) and THF (2 mL) is added a 1.6 M solution of *n*-BuLi in hexanes (0.46 mL, 0.74 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. The solution is cooled to 0 °C, a 0.5 M solution of $ZnCl_2$ in THF (4.70 mL, 2.33 mmol) is added and the solution warmed to ambient temperature and stirred for 30 minute. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) is added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried

over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-60% EtOAc/hexane gradient), followed by a second purification by ISCO column chromatography (100% Et_2O) furnish the title compound (0.07 g, 0.17 mmol, 70%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.06 (s, 3 H), 2.29 (s, 3H), 2.47 (s, 3H), 2.51 (s, 3H), 3.27-3.37 (m, 1H), 3.97 (s, 3H), 6.69 (s, 1H), 8.00 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{28}N_6S$ $(M+H)^+$: 409.6; found: 409.2.

Example 124.

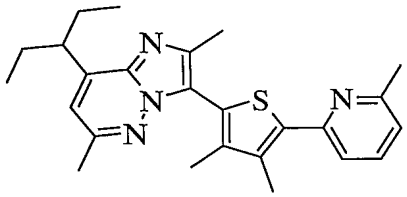
Preparation of 3-(3,4-dimethyl-5-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and THF (1 mL) is added 1.6 M *n*-BuLi (0.16 mL). The solution is stirred for 45 minutes and 0.5 M $ZnCl_2$ in THF (0.52 mL, 0.26 mmol) is added. The solution is warmed to ambient temperature and stirred for 30 minutes. 2-Bromo-thiazole (0.044 mL, 0.49 mmol), and $PdCl_2$(dppf) (0.009 g, 0.012 mmol) are added and the solution heated at 65 °C overnight, diluted with EtOAc (25 mL), washed with sat. NH_4Cl (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient), furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.49 (s, 3H), 2.51 (s, 3H), 2.53 (s, 3H), 3.29-3.39 (m, 1H), 6.68 (s, 1H), 7.35 (d, J = 3.1 Hz, 1H), 7.86 (d, J = 3.1 Hz, 1H). LC/MS (m/z): calcd. for $C_{22}H_{26}N_4S_2$ $(M+H)^+$: 411.6; found: 411.2.

Example 125.

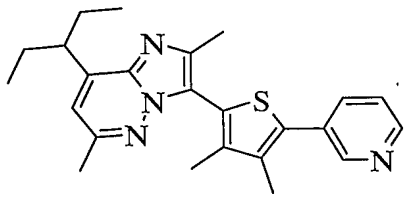
Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $PdCl_2$(dppf) (9 mg, 0.012 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (0.98 mL, 0.49 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-30% EtOAc/hexane gradient) furnish the title compound (0.029 g, 0.069 mmol, 29%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.04 (s, 3 H), 2.45 (s, 3H), 2.47 (s, 3H), 2.50 (s, 3H), 2.59 (s, 3H), 3.29-3.38 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0, 7.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{25}H_{30}N_4S$ $(M+H)^+$: 419.6; found: 419.4.

Example 126.

Preparation of 3-[3,4-dimethyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

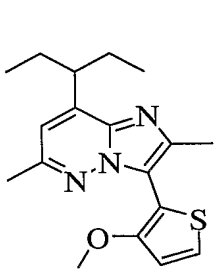


To a –78 °C solution of 3-iodo-pyridine (0.15 g, 0.74 mmol) and 0.5 M $ZnCl_2$ in THF (1.5 mL, 0.75 mmol) is added *t*-BuLi (0.88 mL, 1.49 mmol). The slurry is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3,4-dimethyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.10 g, 0.25 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) are added and the solution stirred at ambient

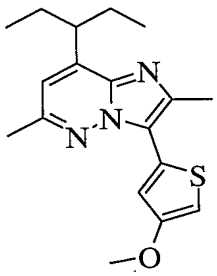
temperature for 2 days, diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-30% EtOAc/hexane gradient) furnish the title compound (6.1 mg, 0.015 mmol, 6%). ^1H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.07 (s, 3 H), 2.29 (s, 3H), 2.49 (s, 3H), 2.53 (s, 3H), 3.30-3.39 (m, 1H), 6.68 (s, 1H), 7.36 (dd, J = 8.0, 4.5 Hz, 1H), 7.79-7.83 (m 1H), 8.57 (d, J = 4.5 Hz, 1H), 8.79 (d, J = 0.9 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.6; found: 405.2.

Example 127 & 128.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 8-(1-ethyl-propyl)-3-(4-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Ex. 127.



Ex. 128.

To a solution of 3-methoxy-thiophene (2.19 g, 19.14 mmol) in Et_2O (50 mL) is added 1.6 M *n*-BuLi (12.20 mL, 19.46 mmol). The solution is heated at a reflux for 30 minutes and cooled to ambient temperature. As solution of 0.5 M $ZnCl_2$ (38.9 mL, 19.5 mmol) and THF (50 mL) is added and the solution is stirred for 30 minutes. 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.0 g, 6.38 mmol) and $PdCl_2$(dppf) (0.23 g, 0.032 mmol) are added and the solution is heated at 65 °C for 4 hours, diluted with EtOAc (250 mL), washed with sat. NH_4Cl (250 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (10%-25% EtOAc/hexane gradient) furnish the title compounds (1.50 g, 4.55 mmol, 71%) and (0.23 g, 0.70 mmol, 11%), respectively.

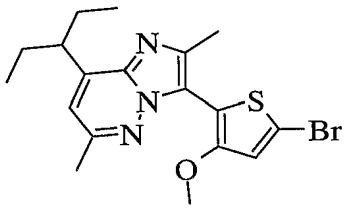
Example 127: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.59 (s, 3H), 2.70 (s, 3H), 3.26-3.35 (m, 1H), 3.86 (s, 3H), 6.32 (d, J = 1.6 Hz, 1H), 6.67 (s, 1H),

7.41 (d, J = 1.6 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 128: ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.5 Hz, 6H), 1.71-1.88 (m, 4H), 2.47 (s, 3H), 2.49 (s, 3H), 3.26-3.35 (m, 1H), 3.84 (s, 3H), 6.62 (s, 1H), 6.96 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H). LC/MS (m/z): calcd. for $C_{18}H_{23}N_3OS$ $(M+H)^+$: 330.5; found: 330.3.

Example 129.

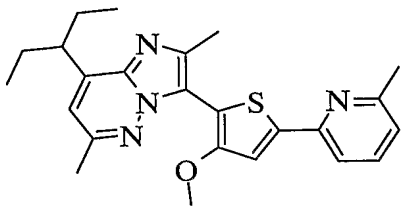
Preparation of 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.78 g, 2.37 mmol) and CH_2Cl_2 (10 mL) is added NBS (0.44 g, 2.49 mmol). The solution is stirred for 1 hour, washed with water (3 x 10 mL), concentrated and purified by ISCO column chromatography (5%-15% EtOAc/hexane gradient) to furnish the title compound (0.87 g, 2.13 mmol, 90%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.82 (s, 3H), 6.65 (s, 1H), 6.97 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}BrN_3OS$ $(M+H)^+$: 408.1; found: 408.3.

Example 130.

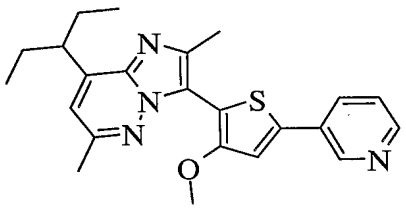
Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol) is added a solution of 0.5 M 6-methyl-2-pyridylzinc bromide in THF (3.0 mL, 1.47 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.066 g, 1.57 mmol, 31%). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.50 (s, 3 H), 2.51 (s, 3H), 2.55 (s, 3H), 3.26-3.37 (m, 1H), 3.90 (s, 3H), 6.63 (s, 1H), 6.99 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.54 (dd, J = 7.4, 7.7 Hz, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4OS$ $(M+H)^+$: 421.6; found: 422.4.

Example 131.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-pyridin-3-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

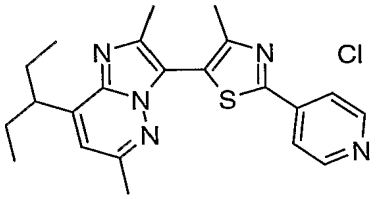


To a –78 °C solution of 3-iodo-pyridine (0.32 g, 1.56 mmol) and 0.5 M $ZnCl_2$ in THF (3.20 mL, 1.59 mmol) is added *t*-BuLi (2.27 mL, 3.85 mmol). The solution is warmed to ambient temperature and stirred for 30 minutes. 3-(5-bromo-3-methoxy-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.26 g, 0.64 mmol) and $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) are added and the solution heated at 50 °C for 1 hour, cooled to ambient temperature and stirred overnight. The solution is diluted with EtOAc (30 mL), washed with sat. NH_4Cl (2 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (20%-50% EtOAc/hexane gradient), furnish the title compound (0.16 g, 0.39 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.91 (m, 4H), 2.52 (s, 3 H), 2.55 (s, 3H), 3.28-3.38 (m, 1H), 3.93, (3H), 6.67 (s, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.31-7.36 (m, 1H), 7.88-

7.92 (m, 1H), 8.55 (d, J = 4.5 Hz, 1H), 8.92 (d, J = 1.8 Hz, 1H). LC/MS (m/z): calcd. for $C_{23}H_{26}N_4OS$ $(M+H)^+$: 407.6; found: 407.4.

Example 132.

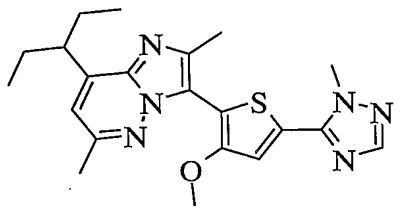
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-pyridin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



A mixture of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (500 mg, 1.27 mmol), 4-pyridineboronic acid (500 mg, 4 mmol), $Pd(PPh_3)_4$ (100 mg, 0.08 mmol), toluene (2 mL), MeOH (1mL), and K_2CO_3 (2 M aqueous solution, 3.5mL) is heated at 100 °C for 18 hours. Ethyl acetate (20mL) is added, and the organic layer is separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification is performed via silica gel chromatography using a 3:1 mixture of hexanes and ethyl acetate to obtain the free amine of the title compound (200 mg, 40%). The purified product is dissolved in ethyl acetate and a freshly prepared solution of hydrogen chloride (0.5 M in ethyl acetate, 2 mL) is added. The solvent is removed in vacuo to give the title compound ^{1}H-NMR ($CDCl_3$), δ 8.2 (m, 2H); 7.05 (m,2H); 6.55 (s, 1H); 3.24 (m, 1H); 2.43 (s, 3H); 2.40 (s, 3H); 2.33 (s, 3H); 1.76 (m, 4H); 0.80 (t, 6H) ppm. MS/ES$^+$ = 391 (100%, M+1).

Example 133.

Preparation of 8-(1-ethyl-propyl)-3-[3-methoxy-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-Bromo-1-methyl-*1H*-[1,2,4]triazole.

To a –78 °C solution of 1-methyl-*1H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution is warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

B. 8-(1-Ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-3-(3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.75 g, 2.28 mmol) and CH_3CN (10 mL) is added NIS (0.54 g, 2.39 mmol). The solution is stirred overnight, concentrated, diluted with EtOAc (30 mL), washed with water (30 mL), sat. NH_4Cl (30 mL), 20% ($NaHSO_3$) (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.91 g, 2.00 mmol, 88%). ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 6H), 1.71-1.89 (m, 4H), 2.46 (s, 3H), 2.52 (s, 3H), 3.25-3.35 (m, 1H), 3.83 (s, 3H), 6.64 (s, 1H), 7.12 (s, 1H). LC/MS (m/z): calcd. for $C_{18}H_{22}IN_3OS$ $(M+H)^+$: 456.4; found: 456.0.

C. 5-Bromo-1-methyl-1*H*-[1,2,4]triazole.

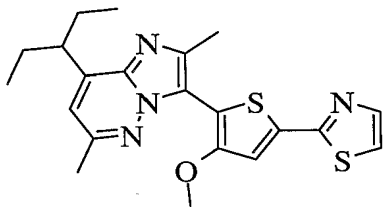
To a –78 °C solution of 1-methyl-1*H*-[1,2,4]triazole (1.0 mL, 13.20 mmol) and THF (100 mL) is added 1.6 M *n*-BuLi (8.70 mL, 13.86 mmol). After 45 minutes 1,2-dibromo-1,1,2,2-tetrafluoro-ethane (1.76 mL, 14.52 mmol) is added, the solution warmed to ambient temperature and stirred for 2 hours. The solution is diluted with EtOAc (200 mL), washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.37 g, 8.46 mmol, 64%). ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.78 (s, 1H). LC/MS (m/z): calcd. for $C_3H_4BrN_3$ $(M+H)^+$: 162.0; found: 161.9.

D. 8-(1-Ethyl-propyl)-3-[3-methoxy-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a slurry of 0.05 g/ mL of Reike® Zn in THF (2.8 mL, 2.11 mmol) is added 5-bromo-1-methyl-*1H*-[1,2,4]triazole and THF (2 mL). The solution is heated at 65 °C for 1 hour, cooled to ambient temperature and the excess Zn allowed to settle for 1 hour. The solution is transferred to a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 0.70 mmol) and $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL) washed with sat. NH_4Cl (30 mL). The aqueous phase is extracted with EtOAc (20 mL). The combined organic layers are dried over $MgSO_4$, filtered and concentrated. The reside is purified by ISCO column chromatography (20%-65% EtOAc/hexane gradient) followed by ISCO column chromatography (100% Et_2O) furnish the title compound (0.19 g, 0.46 mmol, 62%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.51 (s, 3 H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.92 (s, 3H), 4.15 (s, 3H), 6.67 (s, 1H), 7.48 (s, 1H), 7.89 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{26}N_6OS$ $(M+H)^+$: 411.5; found: 411.3.

Example 134.

Preparation of 8-(1-ethyl-propyl)-3-(3-methoxy-5-thiazol-2-yl-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

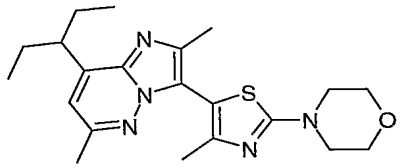


To a flask containing 8-(1-ethyl-propyl)-3-(5-iodo-3-methoxy-thiophen-2-yl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.45 g, 0.99 mmol) and $PdCl_2$(dppf) (0.057 g, 0.078 mmol) is added a 0.5 M solution of 2-thiazolylzinc bromide (9.9 mL, 4.94 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (50 mL), washed with sat. NH_4Cl (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO column chromatography (15%-20% EtOAc/hexane gradient) furnish the title compound (0.29 g, 0.70 mmol, 71%). ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-

1.90 (m, 4H), 2.51 (s, 3H), 2.53 (s, 3H), 3.28-3.37 (m, 1H), 3.93 (s, 3H), 6.67 (s, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.41 (s, 1H), 7.80 (d, J = 3.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{21}H_{24}N_4OS_2$ $(M+H)^+$: 413.6; found: 414.3.

Example 135.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-2-morpholin-4-yl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.



110 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.28 mmol) and 122 mg of morpholine (1.4 mmol) are dissolved in 3.0 ml of THF and 182 mg of cesium carbonate (0.56 mmol) is added. The mixture is put in 4 ml vial with a Teflon® lined cap and heated at 110°C overnight. The reaction mixture is concentrated and applied to a silica-gel column chromatography column with hexane:EtOAc = 3:1 eluent to give 98 mg of the title compound (88%). mass spectrum (m/e): 400(M+1); ^{1}H-NMR(CDCl3): δ 6.70(s, 1H), 3.87(t, 4H, J=4.8Hz), 3.56(t, 4H, J=4.8Hz), 3.35(m, 1H) 2.56(s, 3H), 2.46(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.6Hz)

The following compounds are prepared essentially as described in Example 135. with 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
136.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	2M Methyl-amine/THF	6.71 (s, 1H), 5.44 (s, NH), 3.35 (m, 1H), 3.06 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H).	344
137.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dimethylamine	2M Dimethyl-amine/THF	6.70 (s, 1H), 3.36 (m, 1H), 3.17 (s, 6H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	358
138.	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine	N-Methyl-ethylamine	6.70 (s, 1H), 3.59 (q, J = 7.6 Hz, 2H), 3.37 (m, 1H), 3.15 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.5 Hz, 2H), 0.90 (t, J = 7.1 Hz, 6H).	372
139.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-diethylamine	Diethyl-amine	6.71 (s, 1H), 3.56 (q, J = 7.1 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.30 (t, J = 7.3 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	386

140.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(furan-2-ylmethyl)-methylamine	N-Methyl-(furan-2-yl)-methyl-amine	7.44 (s, 1H), 6.69 (s, 1H), 6.38 (s, 2H), 4.72 (s, 2H), 3.36 (m, 1H), 3.14 (s, 3H), 2.57 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).	424
141.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine	Thio-morpholine	6.71 (s, 1H), 3.92 (m, 4H), 3.37 (m, 1H), 2.80 (m, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	416
142	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-amine	2-methoxy-ethylamine	6.71 (s, 1H), 5.90 (s, NH), 3.66 (t, J = 5.4 Hz, 2H), 3.56 (t, J = 4.6 Hz, 2H), 3.44 (s, 3H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	388
143	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	i-propyl-amine	6.69 (s, 1H), 5.15 (s, NH), 3.74 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 1.35 (d, J = 5.4 Hz, 6H), 0.90 (t, J = 7.4 Hz, 6H).	372
144.	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-pyrrolidine	Pyrrolidine	6.68 (s, 1H), 3.55 (m, 4H), 3.36(m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 2.09 (m, 4H), 1.86 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).	384

145.	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	n-propyl-amine	6.70 (s, 1H), 5.21 (s, NH), 3.39 (t, J = 7.2 Hz, 2H), 3.29 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.85 (m, 4H), 1.74 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H).	372
146	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-benzylamine	Benzyl-amine	7.47-7.23 (m, 5H), 6.70 (s, 1H), 5.52 (s, NH), 6.70 (s, 2H), 3.34 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.19 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H).	420
147	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxy-ethyl)-ethylamine	N-(2-Methoxy-ethyl)-ethylamine		416
148	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methoxy-ethyl)-n-propylamine	N-(2-meth-oxyethyl)-n-propyl-amine	6.69 (s, 1H), 3.72 (m, 4H), 3.47 (t, J = 7.4 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.16 (s, 3H), 1.87 (m, 6H), 0.99 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	430
149	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidine	piperidine	6.68 (s, 1H), 3.53 (t, J = 4.7 Hz, 4H), 3.36 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.86 (m, 4H), 1.71 (m, 6H), 0.90 (t, J = 7.4 Hz,	398

			6H).	
150	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-pentylamine	3-amino-pentane	6.70 (s, 1H), 5.24 (s, NH), 3.32 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.94 (s, 3H), 1.85 (m, 4H), 1.72 (m, 2H), 1.60 (m, 2H), 1.02 (t, J = 7.5 Hz, 6H), 0.90 (t, J = 7.3 Hz, 6H).	400
151	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-cyclo-propylamine	Cyclo-propylamine	6.70 (s, 1H), 6.51 (s, NH), 3.35 (m, 1H), 2.67 (m, 1H), 2.57(s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H), 0.82 (m, 2H), 0.77 (m, 2H).	370
152	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-allylamine	Allylamine	6.70 (s, 1H), 6.0 (m, 1H), 5.60 (s, NH), 5.38 (dd, J = 1.3, 17.4 Hz, 1H), 5.27 (dd, J = 1.2, 10.3 Hz, 1H), 4.0 (d, J = 5.2 Hz, 2H), 3.45 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 6.8 Hz, 6H).	370
153	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,2,3,6-tetra-hydro-pyridine	1,2,3,6-tetra-hydro-pyridine	6.70 (s, 1H), 5.96 (m, 1H), 5.81 (m, 1H), 4.02 (t, J = 3.1 Hz, 2H), 3.72 (t, J = 5.5 Hz, 2H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.35 (m, 2H), 2.19 (s, 3H), 1.87 (m,	396

			4H), 0.90 (t, J = 7.4 Hz, 6H).	
154	N-Ethyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-ethyl-n-propyl-amine	6.69 (s, 1H), 3.58 (q, J = 7.1 Hz, 2H), 3.43 (t, J = 7.5 Hz, 2H), 3.36 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.80 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 6H).	400
155	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-n-propylamine	N-methyl-n-propyl-amine	6.68 (s, 1H), 3.46 (t, J = 8.3 Hz, 2H), 3.35 (m, 1H), 3.16 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.80 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	386
156	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isopropyl-amine	N-Methyl-2-propyl-amine	6.70 (s, 1H), 4.40 (m, 1H), 3.36 (m, 1H), 2.99 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 1.29 (d, J = 6.4 Hz, 6H), 0.90 (t, J = 7.1 Hz, 6H).	386
157	N-Methyl-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-2-propyn-1-amine	N-Methyl-2-Propyn-1-amine	6.70 (s, 1H), 4.40 (d, J = 2.5 Hz, 2H), 3.35 (m, 1H), 3.17 (s, 3H), 2.56 (s, 3H), 2.45 (s, 3H), 2.34 (m, 1H), 2.19 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	382

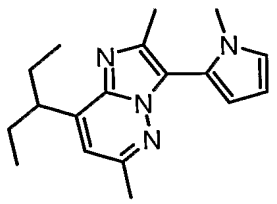
158	N-Methyl-N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-3-amino-propionitrile	N-Methyl-3-amino-propio-nitrile	6.71 (s, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.37 (m, 1H), 3.25 (s, 3H), 2.9 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (s, 3H), 2.18 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).	397
159	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- cyclopropyl-methylamine	Cyclo-propyl-methyl-amine	6.68 (s, 1H), 5.35 (s, NH), 3.34 (m, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.86 (m, 4H), 1.19 (m, 1H), 0.91 (t, J = 7.1 Hz, 6H), 0.61 (m, 2H), 0.31 (m, 2H).	384
160	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(2-methylsulfanyl)-ethylamine	2-methyl-sulfanyl-ethylamine	6.72 (s, 1H), 5.58 (s, NH), 3.58 (m, 2H), 3.35 (m, J = 7.3, 14.4, 1H), 2.85 (m, 2H), 2.57 (s, 3H), 2.46 (s, 3H), 2.17 (s, 6H), 1.85 (m, 4H), 0.90 (t, J = 6.7 Hz, 6H).	404
161	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine	N-{[1,3]di-oxolan-2-yl-methyl}-methyl-amine	6.72 (s, 1H), 5.22 (m, 1H), 4.05 (m, 2H), 3.94 (m, 2H), 3.73 (d, J = 4.5 Hz, 2H), 3.35 (m, J = 6.6, 14.1 Hz, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.84 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).	430
162	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-	N-Methyl-2-propen-1-yl-amine	6.71 (s, 1H), 5.93 (m, 2H), 5.30 (m, 2H), 4.16 (d, J = 5.9 Hz, 2H), 3.39 (m, 1H),	384

	3-yl]-4-methyl-thiazol-2-yl}- N-Methyl-2-propen-1-yl-amine		3.12 (s, 3H), 2.58 (s, 3H), 2.48 (s, 3H), 2.20 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).	
163	(R)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(R)-(tetrahydro-furan-2-ylmethyl)-amine	6.70 (s, 1H), 5.44 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 2H), 0.90 (t, J = 7.3 Hz, 6H).	414
164	(S)-N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(tetrahydro-furan-2-ylmethyl)-amine	(S)-(tetrahydro-furan-2-ylmethyl)-amine	6.69 (s, 1H), 5.45 (s, NH), 4.20 (m, 1H), 3.94 (m, 1H), 3.84 (m, 1H), 3.59 (m, 1H), 3.34 (m, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H), 2.08 (m, 1H), 1.98 (m, 2H), 1.85 (m, 4H), 1.73 (m, 1H), 0.90 (t, J = 7.2 Hz, 6H).	414
165	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-(2-methoxyethyl)-methylamine	N-Methyl-2-methoxy-ethyl-amine	6.70 (s, 1H), 3.74 (t, J = 4.2 Hz, 2H), 3.71 (t, J = 4.1 Hz, 2H), 3.43 (s, 3H), 3.37 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.18 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	402
166	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-	N-Methyl-benzyl-amine	7.43-7.32 (m, 5H), 6.69 (s, 1H), 4.76 (s, 2H), 3.35 (m, 1H), 3.10 (s, 3H), 2.57(s, 3H), 2.48 (s, 3H), 2.21 (s,	434

	yl}-N-methyl-benzylamine		3H), 1.85 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).	
167	N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethyl-benzylamine	N-Ethyl-benzyl-amine	7.41-7.31 (m, 5H), 6.68 (s, 1H), 4.76 (s, 2H), 3.54 (q, J = 7.3, 2H), 3.36 (m, 1H), 2.56(s, 3H), 2.49 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.1 Hz, 6H).	448
168	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-(1-methoxy-2-butyl)-amine	1-Methoxy-2-amino-butane		416
169	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-isobutylamine	N,2-Di-methyl- n-propyl-amine		400
170	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-isobutyl-amine	2-Methyl-n-propyl-amine		386

Example 171.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine.



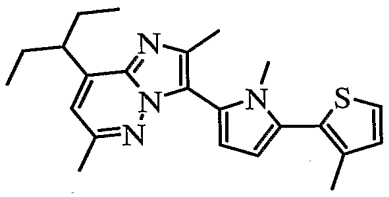
A THF solution (10 mL) of N-methylpyrrole (Aldrich, 800 μL, 9.0 mmol) is cooled to -78 °C under N_2 then treated with *tert*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol). The solution is warmed to room temperature for 30 minutes then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 18 mL, 9.0 mmol). The resulting mixture is warmed to room temperature and treated with a THF slurry (5 mL) containing 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.02 gm, 3.0 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 140 mg, 0.17 mmol). The mixture is heated to 60 °C overnight, then poured into sat'd aq NH_4Cl (50 mL) and extracted with diethyl ether (75 mL). The organic extract is ished with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (407.5 mg, 46% yield) as an oil.

ES-MS (m/z): calc'd for $C_{18}H_{24}N_4$: 296.20; found 297.5 $(M+H)^+$

^1H NMR (400 mHz, $CDCl_3$): δ 6.86 (s, 1H), 6.65 (s, 1H), 6.32-6.28 (m, 2H), 3.50 (s, 3H), 3.35 (br s, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 1.87-1.75 (m, 4H), 0.87 (t, J = 7.0 Hz, 6H).

Example 172.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.



A. 3-(5-Bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

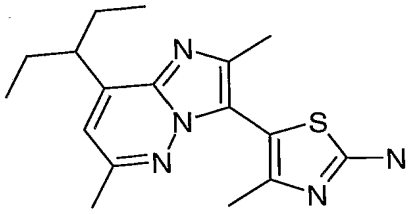
A THF solution (10 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(1-methyl-^1H-pyrrol-2-yl)-imidazo[*1,2-b*]pyridazine (414 mg, 1.40 mmol) is cooled to 0 °C and treated with a THF solution of NBS (250 mg, 1.40 mmol). Within 5 min, the reaction mixture is treated with sat Na_2SO_3 (1 mL) then concentrated. The resulting residue is diluted with ethyl acetate (50 mL) and ished with 50% aq sat'd Na_2SO_3 (2x50 mL). The organic extract is dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (374 mg, 71% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{23}BrN_4$: 374.11; found 375 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.33 (d, J = 4.0 Hz, 1H), 6.30 (d, J = 4.0 Hz, 1H), 3.40 (s, 3H), 3.36 (br s, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, J = 7.3 Hz, 6H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[1-methyl-5-(3-methyl-thiophen-2-yl)-^1H-pyrrol-2-yl]- imidazo[*1,2-b*]pyridazine.

A THF slurry (5 mL) of 3-(5-bromo-1-methyl-^1H-pyrrol-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (143 mg, 0.38 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 19 mg, 0.023 mmol) is treated with 3-methyl-2-thienyl zinc bromide (Aldrich, 0.5 M in THF, 3.8 mL, 1.9 mmol) then heated to 60 °C for 1 hr. The resulting mixture is poured into sat'd NH_4Cl (25 mL) and extracted with diethyl ether (35 mL). The organic extract is washed with aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 15% ethyl acetate in hexane) to elute the product. The material is purified a second time by flash chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the product. Only the fractions containing pure desired product, as judged by MS analysis, are collected and give the title compound (82.6 mg, 55% yield) as an oil. ES-MS (m/z): calc'd for $C_{23}H_{28}N_4S$: 392.20; found 393.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.28 (d, J = 5.3 Hz, 1H), 6.96 (d, J = 4.8 Hz, 1H), 6.67 (br s, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 4.0 Hz, 1H), 3.35 (br s, 1H), 3.33, (s, 3H), 2.52 (s, 3H), 2.51 (s, 3H), 2.26 (s, 3H), 1.89-1.76 (m, 4H), 0.87 (t, J = 7.5 Hz, 6H).

Example 173.

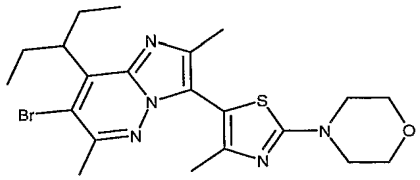
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-ylamine.



50 mg of 8-(1-ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.13 mmol) and 10 mg of copper (I) oxide are added to 3 ml of 2 M NH3 in MeOH and vial is capped with a Teflon® lined cap, heated at 130°C for overnight. The reaction mixture is concentrated under N2 gas and applied onto a silica-gel chromatography column (Hexane: AcOEt: 2 M NH3 in MeOH = 20:20:1) to give 22 mg of the title compound. Yield 54%: mass spectrum (m/e): 330(M+1); ^{1}H-NMR(CDCl3): 6.72(s,1H), 5.24(br, 2H), 3.40(m, 1H), 2.56(s, 3H), 2.47(s, 3H), 2.18(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 174.

Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



A. 7-Bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

547 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-methyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (1.74 mmol) and 341 mg of NBS (1.92 mmol) are dissolved in 20 ml of CHCl3 and stirred at room temperature overnight. The reaction mixture is washed with sat. $Na_2S_2O_3$, sat. NaCl, dried over Na_2SO_4 and evaporated. The crude materials are

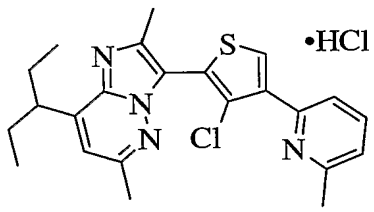
applied onto a silica-gel chromatography column (Hexane:AcOEt=8:1) to give 218 mg of the title compound. Yield 27%. mass spectrum (m/e): 473(M+1); ^{1}H-NMR(CDCl3): 3.44(m, 1H), 2.70(s, 3H), 2.45 (s, 3H), 2.37(s, 3H), 2.03(m, 4H), 0.90(m, 6H).

B. N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

72 mg of 7-bromo-3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol) and 66 mg of morpholine (0.76 mmol) and 97 mg of cesium carbonate (0.3 mmol) are put in 4 ml vial with 3 ml of dry THF. The vial is capped with a Teflon® lined cap and heated at 100°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1) to give 30 mg of the title compound. Yield 42%.: mass spectrum (m/e): 479(M+1); ^{1}H-NMR(CDCl3): 3.87(t, 4H, J=5.0Hz), 3.55(t, 4H, J=5.0Hz), 3.45(m, 1H), 2.70(s, 3H), 2.44(s, 3H), 2.40(m, 2H), 2.18(s, 3H), 2.01(m, 2H), 0.88(t, 6H, J=7.3Hz).

Example 175.

Preparation of 3-[3-chloro-4-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

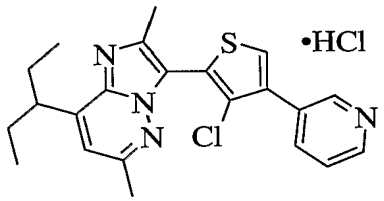


Reike® Zn (0.5 g/ mL solution in THF (1.9 mL,, 1.45 mmol) is added to a flask containing 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.73 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the resulting solution is transferred to a flask containing 2-bromo-6-methyl-pyridine (0.12 g, 0.73 mmol) and $PdCl_2$(dppf) (0.018 g, 0.024 mmol). The reaction is heated at 65 °C overnight, diluted with ethyl acetate (20 mL), and washed with a sat. solution of NH_4Cl (15 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by silica gel chromatography using a hexanes and ethyl acetate gradient. The resulting product is dissolved in

dichloromethane (5 mL), treated with a 1 M solution of HCl in EtOH (0.35 mL, 0.35 mmol) and concentrated. The residue is recrystallized from ethyl acetate and hexanes furnish the title compound (0.033 g, 0.072 mmol, 11%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.3 Hz, 6H), 1.73-2.02 (m, 4H), 2.68 (s, 3H), 2.81 (s, 3H), 3.21 (s, 3H), 3.88-3.98 (m, 1H), 7.25 (s, 1H), 7.65 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 7.5, 7.1 Hz, 1H), 9.26 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{23}H_{26}Cl_2N_4S$ $(M+H)^+$: 424.2; found: 424.2.

Example 176.

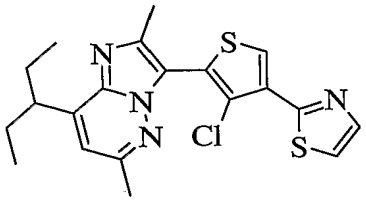
Preparation of 3-(3-chloro-4-pyridin-3-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.97 mmol), Reike® Zn (0.5 g/ mL solution in THF, 2.5 mL, 1.94 mmol), 3-iodo-pyridine (0.30 g, 1.45 mmol), $PdCl_2$(dppf) (0.035 g, 0.048 mmol), and a 1 M solution of HCl in EtOH (0.61 mL, 0.61 mmol) furnish the title compound (0.076 g, 0.17 mmol, 18%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.0 Hz, 6H), 1.71-1.88 (m, 2H), 1.88-2.01 (m, 2H), 2.68 (s, 3H), 2.81 (s, 3H), 3.85-3.96 (m, 1H), 5.28 (s, 1H), 7.27 (bs, 1H), 8.09 (bs, 1H), 8.23 (bs, 1H), 8.70 (bs, 1H), 8.89 (bs, 1H), 9.18 (bs, 1H). LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 177.

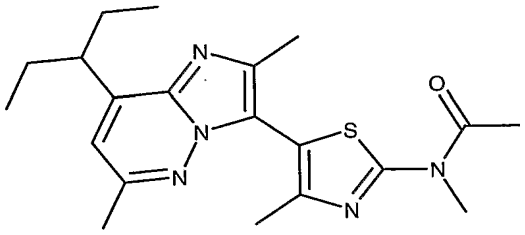
Preparation of 3-(3-chloro-4-thiazol-2-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure analogous to Example 175, 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), Reike® Zn (0.5 g/ mL solution in THF, 1.6 mL, 1.21 mmol), 2-bromo-thiazole (0.11 mL, 1.21 mmol), and $PdCl_2$(dppf) (0.022 g, 0.030 mmol) furnish the title compound (0.012 g, 0.29 mmol, 6.8%). ^{1}H-NMR ($CDCl_3$), δ 0.89 (t, J = 7.5 Hz, 6H), 1.75-1.94 (m, 4H), 2.52 (s, 6H), 3.27-3.43 (m, 1H), 6.73 (s, 1H), 7.43 (d, J = 3.3 Hz, 1H), 7.94 (d, J = 3.3 Hz, 1H), 8.30 (s,1H) ppm. LC/MS (m/z): calcd. for $C_{20}H_{21}ClN_4S_2$ $(M+H)^+$: 417.1; found: 417.2.

Example 178.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methyl-acetamide.

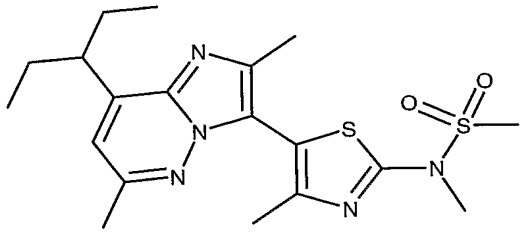


60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH_2Cl_2 and 16 mg of acetylchloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt = 3:1 and Hexane :AcOEt=2:1) to give 33.8 mg of the title compound. Yield 50%: mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.03(s,1H), 3.79(s, 3H),

3.47(m, 1H), 2.54 (s, 3H), 2.47(s, 3H), 2.46(s, 3H), 2.31(s, 3H), 1.86(m, 4H), 0.91(t, 6H, J=7.4Hz).

Example 179.

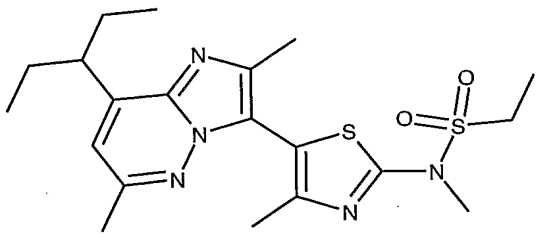
Preparation of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-methanesulfonyl-methylamine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.17 mmol) and 86 mg of triethylamine (0.85 mmol) are dissolved in 3.0 ml of CH2Cl2 and 23 mg of methanesulfonyl chloride (0.2 mmol) is added. The vial is capped with a Teflon® lined cap and shaken at room temperature for 2h. The reaction mixture is concentrated and applied to silica-gel chromatography (Hexane :AcOEt = 2:1) to give 53.8 mg of the title compound. Yield 75%. mass spectrum (m/e): 422(M+1); ^{1}H NMR(CDCl3): 6.96(s, 1H), 3.60(s, 3H), 3.34(m, 1H), 3.19(s, 3H), 2.56(s, 3H), 2.48(s, 3H), 2.29(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.4Hz).

Example 180.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-N-ethanesulfonyl-methylamine.

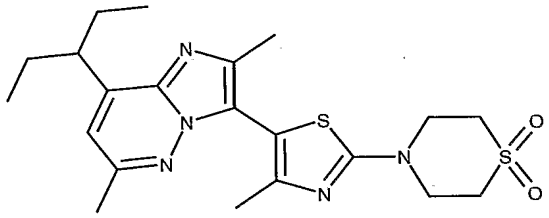


The title compound is prepared by a procedure analogous to Example 178. employing 50 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methylamine (0.15 mmol), 51 mg of triethylamine (0.5 mmol) and 39 mg of ethanesulfonylchloride (0.3 mmol). 48.9 mg, Yield 75%: mass spectrum

(m/e): 436(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.62(s, 3H), 3.42(q, 2H, J=7.4Hz), 3.35(m, 1H), 2.55(s, 3H), 2.48(s, 3H), 2.28(s, 3H), 1.85(m, 4H), 1.46(t, 3H, J=7.4Hz), 0.90(t, 6H, J=7.5Hz).

Example 181.

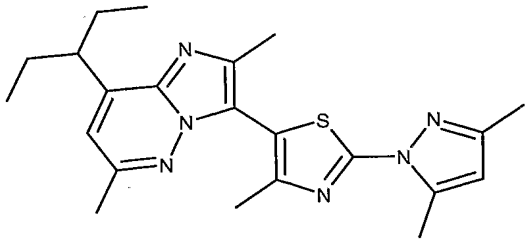
Preparation of 3-[2-(1,1-dioxo-thiomorpholin-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



60 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}thiomorpholine(0.14 mmol) is dissolved in 3 ml of CH_2Cl_2 and 62 mg of mCPBA (0.36 mmol) is added. The reaction mixture is stirred at room temperature for 30 min. The reaction mixture is diluted with CH_2Cl_2, washed with sat. NaHCO3 and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt:2 M NH3 in MeOH=10:3:1) to give 20.3 mg of the title compound. Yield 33%: mass spectrum (m/e): 448(M+1). ^{1}H-NMR: 6.72 (s, 1H), 4.16 (t, J = 4.7 Hz, 4H), 3.35 (m, 1H), 3.23 (t, J = 5.2 Hz, 4H), 2.57 (s, 3H), 2.48 (s, 3H), 2.19 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).

Example 182.

Preparation of 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine.

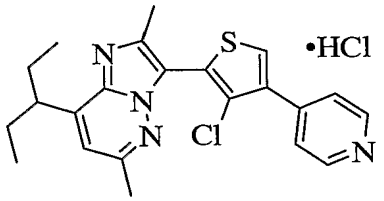
The title compound is prepared essentially as described in Example 135 using hydrazine. MS found (M+1) 345.

B. 3-[2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

28 mg of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-hydrazine (0.08 mmol) and 80 mg of 2,4-pentanedione (0.8 mmol) are dissolved in 1.0 ml of AcOH and heated at 100°C for 2 h. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : AcOEt = 5:1) to give 23 mg of the title compound. Yield 70%: mass spectrum (m/e): 409 (M+1). 6.72 (s, 1H), 6.03 (s, 1H), 3.36 (m, J = 7.1, 14.1 Hz, 1H), 2.75 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.32(s, 3H), 2.31(s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H).

Example 183.

Preparation of 3-(3-chloro-4-pyridin-4-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, hydrochloride salt.

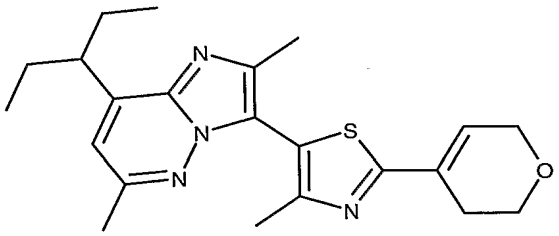


A solution of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 0.61 mmol), 4-pyridyl-boronic acid (0.82, 0.67 mmol), a 2 M solution of Na_2CO_3 (0.5 mL, 0.91 mmol), and *n*-PrOH (2.5 mL) are degassed with nitrogen for 10 minutes. $Pd(OAc)_2$ (0.0027 g, 0.012 mmol) and PPh_3 (0.0095 g, 0.036 mmol) are added, and the solution heated at a 90 °C overnight. The solution is diluted with ethyl acetate (40 mL) and washed with a 10 % solution of Na_2CO_3 (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-30% EtOAc gradient). The resulting product is dissolved in dichloromethane (5 mL), treated with a 1 M solution of HCl in

EtOH (0.35 mL, 0.35 mmol), and concentrated. The residue is recrystallized from acetonitrile and ethyl acetate furnish the title compound (0.15 g, 0.34 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 0.95 (t, J = 7.5 Hz, 6H), 1.73-1.88 (m, 2H), 1.89-2.04 (m, 2H), 2.68 (s, 3H), 2.82 (s, 3H), 3.87-3.97 (m, 1H), 7.28 (s, 1H), 8.26-8.34 (m, 3H), 8.95 (d, J = 5.3 Hz, 2H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{24}Cl_2N_4S$ $(M+H)^+$: 411.1; found: 411.2.

Example 184.

Preparation of 3-[2-(3,6-dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol.

370 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.93 mmol) is dissolved in 10 ml of dry THF and cooled to –78°C. 0.6 ml of n-BuLi 2.0 M in hexane (1.2 mmol) is added and stirred at –78°C for 30 min. 141 mg of tetrahydro-*4H*-pyran-4-one (1.41 mmol) is added and stirred at –78°C for 2 h. The reaction mixture is diluted with AcOEt, washed with sat. NH4Cl , dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt : 2 M NH3 in MeOH =10:3:1) to give 152 mg of the title compound. Yield 40%.: mass spectrum (m/e): 415(M+1). ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H), 3.99 (t, J = 2.2 Hz, 4H), 3.97 (t, J = 2.2 Hz, 4H), 3.35 (m, 1H), 3.20 (s, OH), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 1.88 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H).

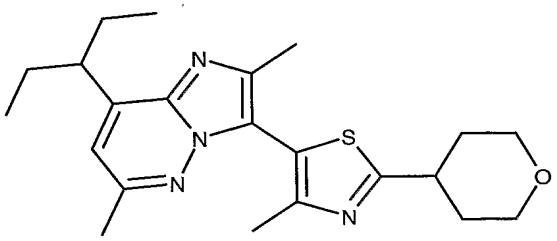
B. 3-[2-(3,6-Dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

150 mg of 4-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-tetrahydro-pyran-4-ol (0.36 mmol) is dissolved in 5 ml of CH2Cl2

and 112 mg of triethylsilane (0.96 mmol) and 717 mg of trifluoroacetic acid (6.3 mmol) are added. The reaction mixture is stirred at room temperature for 1h. The reaction mixture is stirred under reflux for 1 h and cooled down to room temperature. The solvent is removed in *vacuo*. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt: 2 M NH3 in MeOH =10:3:1) to give 64 mg of the title compound. Yield 45%. mass spectrum (m/e): 397(M+1). 6.94 (s, 1H), 6.71 (s, 1H), 4.41 (d, J = 2.6 Hz, 2H), 3.98 (t, J = 5.3 Hz, 2H), 3.43 (m, 1H), 2.62(s, 3H), 2.75 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.86 (m, 4H), 0.92 (t, J = 8.2 Hz, 6H).

Example 185.

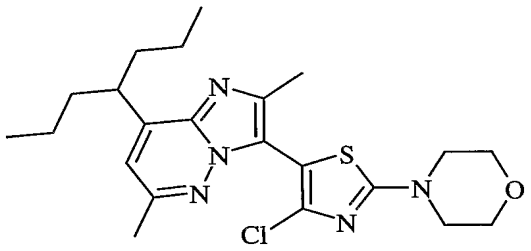
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[4-methyl-2-(tetrahydro-pyran-4-yl)-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine.



Add 3-[2-(3,6-dihydro-*2H*-pyran-4-yl)-4-methyl-thiazol-5-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (55 mg, 0.14 mmol), 5% palladium on carbon (55 mg) and absolute ethanol (50 ml) to a pressure vessel. Purge the reaction vessel with nitrogen, purge the reaction vessel with hydrogen, pressurize the reaction mixture with hydrogen (415 KPa), seal the vessel, agitate the reaction and heat to 40 °C. Continue the reaction for 18 hours then turn off the heat and allow the reaction mixture to cool to ambient temperature. Vent the excess hydrogen from the vessel and purge the vessel with nitrogen. Filter the reaction mixture to remove the 5% palladium on carbon. The filtrate is concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt : 2 M NH_3 in MeOH = 10:3:1) to give 12.8 mg of the title compound. Yield 23%. mass spectrum (m/e): 399(M+1). ^{1}H NMR ($CDCl_3$): δ 6.73 (s, 1H), 4.14 (m, 2H), 3.60 (m, 2H), 3.34 (m, 2H), 2.56 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 186.

Preparation of 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



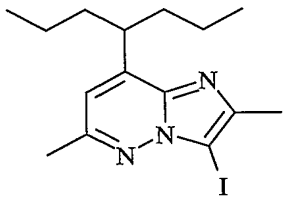
A. 6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine.

6-Methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine can be made using chemistry described in J. Heterocylic Chem. **1991**, *28*, 583. A 250 mL three neck round bottom flask is charged with 3-amino-6-methyl pyridazine (2.5 g, 0.229 moles, 1.0 equiv), water (70 mL), and acetonitrile (50 mL). Concentrated sulfuric acid (3.51 g, 1.91 mL, 0.0344 moles, 1.5 equiv), silver nitrate (3.87 g, 0.0229 moles, 1.0 equiv), and valproic acid (7.21 g, 7.95 mL, 0.050 moles, 2.2 equiv) are added to the reaction mixture. The reaction is heated to 75 °C. As the reaction mixture is heating, a solution of $(NH_4)_2S_2O_8$ (7.85 g, 0.0344 moles, 1.5 equiv) in 40 mL of water is slowly added via an addition funnel over a period of 30 minutes. The reaction mixture is heated at 70-80 °C for two more hours. The reaction mixture is cooled and dichoromethane is added. The reaction is made basic with a 30% aqueous NaOH solution and filtered through a short Celite® plug. The organic layer is separated, and the aqueous layer is extracted two more times with dichoromethane. The combined organic extracts are dried over Na_2SO_4. The solvent is evaporated and the crude material is purified using silica gel chromatography with a 2.0 N solution of NH_3 in MeOH and methylene chloride as eluent. Yield = 0.61 g (13%). MS (APCI): 208 (M+1).

B. 2,6-Dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 250 mL round bottom flask is charged with 6-methyl-4-(1-propyl-butyl)-pyridazin-3-ylamine (0.611 g, 0.00295 moles, 1 equiv), ethanol 2B (30 mL), and chloroacetone (0.382 g, 0.328 ml, 0.00412 moles, 1.4 equiv). The reaction mixture is heated at 75 °C overnight and then cooled to room temp. $NaHCO_3$ (0.371 g, 0.00442 moles, 1.5 equiv) is slowly added to the reaction mixture that is then heated to 100 °C overnight. The reaction mixture is cooled and the solvent is evaporated. Dichloromethane is added and the reaction mixture is passed through filter paper. The solvent is evaporated to obtain a brown oil which is purified via silica gel chromatography. The material is eluted with a hexanes and ethyl acetate gradient to obtain 0.511 g of the final products. Two peaks are identified in the lc/ms. The mixture is used "as is" in the next reaction. MS (APCI): 246 (M+1).

C. 3-Iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



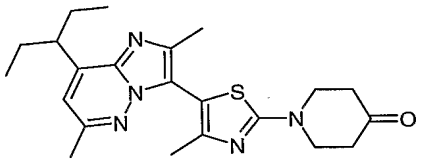
A 50 mL round bottom flask is charged with 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.51 g, 0.0021 moles) and acetonitrile (3 mL). The reaction mixture is placed on an ice bath and NIS (0.468 g, 0.00208 moles) is added neat. The reaction is stirred overnight and the ice bath melts. The next day, the reaction mixture is partitioned between dichloromethane and a saturated aqueous solution of $NaHCO_3$. The organic layer is collected and the aqueous layer is extracted two more times with dichloromethane. The organic extracts are combined, washed with brine, and dried over Na_2SO_4. The solvent is evaporated and the crude material is purified via silica gel chromatography eluting with hexanes and then a 25:75 mixture of ethyl acetate and hexanes. Yield = 0.435 g (56%). MS (APCI): 372 (M+1).

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.

A 15 mL round bottom flask is charged with 3-iodo-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[1,2-*b*]pyridazine (0.200 g, 0.000539 moles), 4-(4-chloro-thiazol-2-yl)-morpholine (0.165 g, 0.000808 moles), Cs_2CO_3 (0.361 g, 0.00108 moles, 2.0 equiv), $Pd(dba)_2$ (0.0092 g, 0.0000161 moles, 0.03 equiv), PPh_3 (0.00847 gram, 0.000323 moles, 0.060 equiv) and DMF (2.0 mL). Nitrogen is bubbled through the reaction mixture for 15 minutes; then, the reaction mixture is heated at 130 °C overnight. The next day, the reaction mixture is partitioned between Et_2O and a saturated solution of NH_4Cl. The aqueous layer is extracted twice more with Et_2O. The organic extracts are combined, washed 2-3 times with H_2O, washed once with brine, and dried over Na_2SO_4. The solvents are evaporated in vacuo and the crude reaction mixture is purified via silica gel chromatography. Yield = 0.1737 g (72%). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7 Hz, 6H), 1.14- 1.37 (m, 4H), 1.74 (q, J = 8 Hz, 4H), 2.54 (s, 3H), 2.50 (s, 3H), 3.48 (m, 1H), 3.53 (t, J = 5 Hz, 4H), 3.83 (t, J = 5 Hz, 4H), 6.71(br s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{30}ClN_5OS$ $(M+H)^+$: 448; found: 448.

Example 187.

Preparation of 1-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.



A. 8-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane.

100 mg of 3-(2-bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.25 mmol), 182 mg of 4-piperidineethylene ketal (1.27 mmol) and 244 mg of Cs2CO3 (0.75 mmol) are put into 4.0 ml vial with 2.0 ml of THF. The vial is capped with a Teflon® lined cap and heated at 110°C for 3 days. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 116 mg of the title compound. Yield 100%. mass spectrum

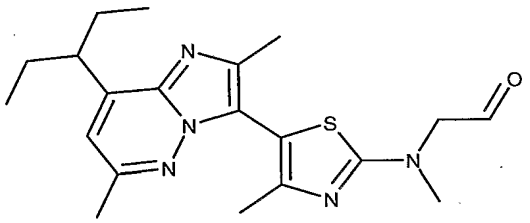
(m/e): 456(M+1). ^{1}H NMR ($CDCl_3$): δ 6.69 (s, 1H), 4.05 (s, 4H), 3.70 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.56 (s, 3H), 2.46 (s, 3H), 2.18 (s, 3H), 1.90-1.78 (m, 8H), 0.90 (t, J = 7.2 Hz, 6H).

B. 1-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-piperidin-4-one.

70 mg of 8-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-1,4-dioxa-8-aza-spiro[4.5]decane (0.15 mmol) is dissolved in 10.ml of conc. HCl and stirred at room temperature for 2 h. The reaction mixture is neutralized with sat. NaHCO3, extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=2:1) to give 33.2 mg of the title compound . Yield 52%. mass spectrum (m/e): 412(M+1). ^{1}H NMR ($CDCl_3$): δ 6.70 (s, 1H), 3.94 (t, J = 6.2 Hz, 4H), 3.35 (m, 1H), 2.67 (t, J = 6.5 Hz, 4H), 2.57 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.1 Hz, 6H).

Example 188.

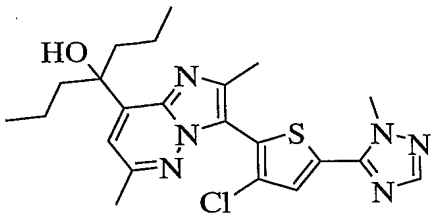
Preparation of ({5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-methyl-amino)-acetaldehyde.



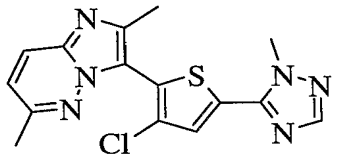
85 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}- N-{[1,3]dioxolan-2-ylmethyl-methylamine (0.2 mmol) is dissolved in 2 ml of conc. HCl and stirred at 50°C for 30 min. The mixture is cooled to room temperature and neutralized with sat. NaHCO3. The mixture is extracted with CH2Cl2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (CH2Cl2:MeOH=20:1) to give 73.4 mg of the title compound. Yield 76%. mass spectrum (m/e): 386(M+1). 9.79 (s, 1H), 6.72 (s, 1H), 4.39 (s, 2H), 3.36 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.47 (s, 3H), 2.20 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).

Example 189.

Preparation of 4-{3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

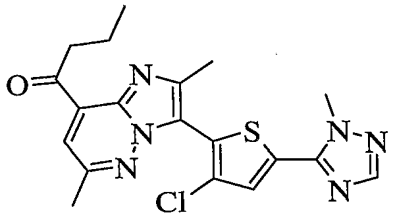


A. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine(0.32 g, 2.17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

B. 1-{3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one.



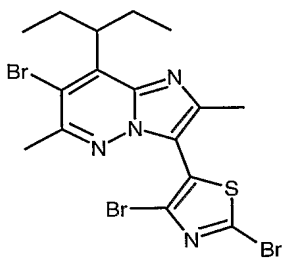
A solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.58 mmol), *N*-methoxy-*N*-methyl-butylamide (Wolberg, M. et. al. *Chem. Europ. J.* 2001, 7, 4562.) (0.084 g, 0.64 mmol) in THF (3 mL) is cooled to a -78 °C, and a 2.0 M solution of LDA in heptane/ THF/ ethyl benzene (0.58 mL, 1.16 mmol) is added. The solution is warmed to ambient temperature, diluted with dichloromethane (20 mL), and washed with a sat. NH_4Cl solution (15 mL). The organic layer is dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-100% EtOAc gradient) to furnish the title compound (0.11 g, 0.27 mmol, 46%). ^{1}H-NMR ($CDCl_3$), δ 1.04 (t, J = 7.0 Hz, 3H), 1.76-1.86 (m, 2H), 2.56 (s, 3H), 2.59 (s, 3H), 3.51 (t, J = 7.1 Hz, 2H), 4.15 (s, 3H), 7.36 (s, 1H), 7.49 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{19}H_{19}ClN_6OS$ $(M+H)^+$: 415.1; found: 415.3.

C. 4-{3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-heptan-4-ol.

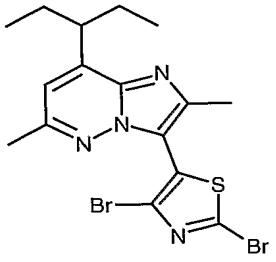
A solution of 1-{3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-8-yl}-butan-1-one (0.15 g, 0.36 mmol) and THF (5 mL) is cooled to 0°C, and a 2.0 M propyl magnesium bromide solution in diethylether (0.22 mL, 0.43 mmol) is added. The reaction is warmed to ambient temperature, diluted with ethyl acetate (30 mL), and washed with a sat. NH_4Cl solution (30 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) to furnish the title compound (0.016 g, 0.017 mmol, 47%). ^{1}H-NMR ($CDCl_3$), δ 0.90 (t, J = 7.4 Hz, 6H), 1.12-1.29 (m, 2H), 1.37-1.54 (m, 2H), 1.86-2.04 (m, 4H), 2.50 (s, 3H), 2.54 (s, 3H), 4.15 (s, 3H), 6.11 (bs, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H) ppm. LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6OS$ $(M+H)^+$: 459.2; found: 459.3.

Example 190, 191, and 192.

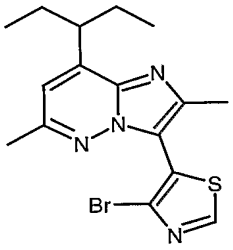
Preparation of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



190.



191.



192.

A. 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

2.41 g (7 mmol) of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine, 3.00 g of thiazole (35.2 mmol), 378 mg of triphenylphosphine (1.44 mmol) and 4.71 g of Cs2CO3 (14.5 mmol) are combined with 25 ml of DMF and N2 gas is bubbled in for 30 min. 330 mg of Pd2dba3 (0.36 mmol) is added and the tube is sealed. The reaction tube is heated at 130°C overnight. To the reaction mixture is added water and CH2Cl2, and the CH2Cl2 layer is separated, washed with sat. NaCl and dried over Na2SO4. The solvents are removed *in vauo* and crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 3:1) to give 1.48 g of the title compound. Yield 70%. mass spectrum (m/e): 301(M+1); ^{1}H-NMR(CDCl3): 8.93(s, 1H), 8.52(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.76(s, 3H), 2.66(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.5Hz).

B. 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine; and 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

1.05 g (3.5 mmol) of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine and 1.56 g of NBS (8.75 mmol) are dissolved in 50 ml of CH2Cl2 and stirred at room temperature for 3 days. The reaction mixture is diluted with CH2Cl2 and washed with sat. $Na_2S_2O_3$ and sat. NaCl. The separated organic layer is dried over Na_2SO_4 and evaporated. The reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 20:1→8:1) to give three products:

149 mg of 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (9%);

936 mg of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (58%); and

77 mg of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (6%).

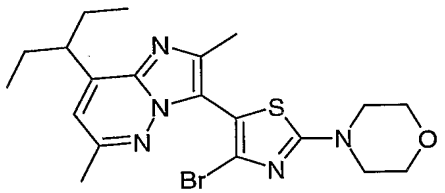
7-Bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 538(M+1); ^{1}H-NMR(CDCl3): 3.45(m, 1H), 2.71(s, 3H), 2.52(s, 3H), 2.38(m, 2H), 2.02(m, 2H), 0.88(t, 6H, J=7.5Hz);

3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 459(M+1); ^{1}H-NMR(CDCl3): 6.79(s, 1H), 5.33(m, 1H), 2.57(s, 3H), 2.55(s, 3H), 1.87(m, 4H), 0.90(t, 6H, J=7.5Hz); and

3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine mass spectrum (m/e): 380(M+1); ^{1}H-NMR(CDCl3): 9.01(s, 1H), 6.77(s, 1H), 3.35(m, 1H), 2.55(s, 3H), 2.54(s, 3H), 1.87(m, 4H), 0.91(t, 6H, J=7.5Hz).

Example 193.

Preparation of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



100 mg (0.22 mmol) of 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 96 mg of morpholine (1.1 mmol) and 215 mg of Cs2CO3(0.66 mmol) are put in a 4 ml vial with dry THF, and the vial is

capped with a Teflon cap. The vial is heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt :2 M NH3 in MeOH = 9:3:1) to give 72.7 mg of the title compound. Yield 71%. mass spectrum (m/e): 465(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.87(t, 4H, J=5.1Hz), 3.58(t, 4H, J=5.1Hz), 3.35(m, 1H), 2.57(s, 3H), 2.53(s, 3H), 1.86(m, 4H), 0.90(t, 6H, J=7.5Hz).

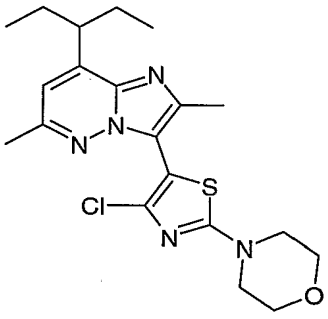
The following compounds are prepared essentially as described in Example 193. Examples 194-197 use 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and the named amine. Example 198. uses 7-bromo-3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and the named amine:

Ex	Name	Amine	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
194	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-methyl-amine	Methyl-amine	6.75 (s, 1H), 5.85 (s, NH), 3.37 (m, 1H), 3.07 (d, J = 5.3 Hz, 3H), 2.59 (s, 3H), 2.55 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.2 Hz, 6H).	409
195	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	Dimethyl-amine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J=7.3Hz)	423
196	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-2-methoxy-ethyl-methyl-amine	6.71 (s, 1H), 3.76 (m, 2H), 3.71 (m, 2H), 3.42 (s, 3H), 3.35 (s, 1H), 3.21 (s, 3H), 2.57(s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	467

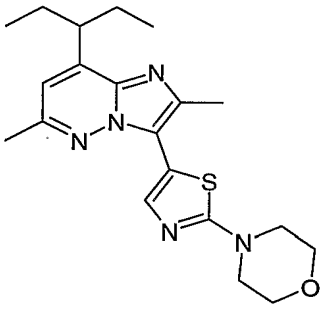
197	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-methyl-i-propyl-amine	6.72 (s, 1H), 4.43 (m, 1H), 3.36 (m, 1H), 3.0 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H), 1.86 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 0.90 (t, J = 7.4 Hz, 6H).	451
198	N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-bromo-thiazol-2-yl}-morpholine	Morpholine	3.87 (t, J = 4.5 Hz, 4H), 3.58 (t, J = 7.8 Hz, 4H), 3.43 (m, 1H), 2.71(s, 3H), 2.50 (s, 3H), 2.38 (m, 2H), 2.01 (m, 2H), 0.88 (t, J = 7.5 Hz, 6H).	544

Example 199 and 200.

Preparation of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine and N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.



199.



200.

Method A

40 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 25 mg of CuCl (0.25 mmol) are put in a 4 ml vial with 2 ml of dry DMF and capped with a Teflon cap. The vial is heated at 120°C overnight. The reaction mixture is filtered, washed with CH2Cl2 and the filtrate is concentrated. The crude product mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 2:1 and Hexane : AcOEt = 8:1) to give two products:

4.2 mg of N-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (12%), and

7.2 mg of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine (22%).

N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 420(M+1); ^{1}H-NMR(CDCl3): 6.73(s, 1H), 3.88(t, 4H, J=5.0 Hz), 3.57(t, 4H, J=5.0Hz), 3.35(m, 1H), 2.57(s, 3H), 2.52(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.5Hz.

N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine mass spectrum (m/e): 386(M+1); ^{1}H-NMR(CDCl3): 7.75(s, 1H), 6.70(s, 1H), 3.91(t, 4H, J=5.0Hz), 3.61(t, 4H, J=5.0Hz), 3.34(m, 1H), 2.67(s, 3H), 2.61(s, 3H), 1.85(m, 4H), 0.88(t, 6H, J=7.5Hz).

Method B N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-morpholine.

A 20L reactor flask under nitrogen is charged with 2900 ml of dry and degassed DMF then with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[1,2-b]pyridazine (287 g, 0.836 mol), 2-morpholino-4-chlorothiazole (205.4 g, 1.01 mol, 1.2 equv.), $Pd(OAc)_2$ (3.74 g, 7.91 mmol, 0.01 equiv.), triphenylphosphine (8.77g, 33.1 mmol, 0.04 equiv.), Copper iodide (8 g, 41.59 mmol, 0.05 equiv.) and cesium carbonate (544.9 g, 1.65 mol). The reaction mixture is heated at 120°C. After 16 h at 120°C, 1.87 g of $Pd(OAc)_2$ and 4.38 g of triphenylphosphine more is added. After 1 h, the mixture is cooled, quenched with NH_4Cl solution (4300 mL) and extracted with MTBE (2900 mL), the aqueous phase is extracted twice more with 2000 ml of MTBE. The organic phases are washed with sat NaCl aq (2000 mL), then treated with charcoal 72 g in flask bottle and filtered on Celite®. The filtrate is concentrated under vacuum to afford 373.8 g (79.3%) of the title compound which is 81.4%-area HPLC analysis the rest being solvent and with no detectable Example 200 by-product.

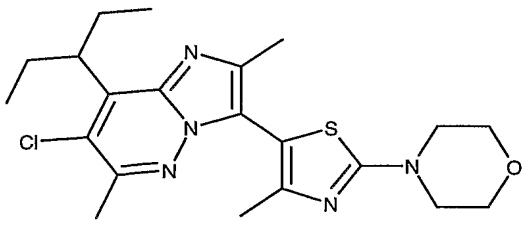
The following title compounds are prepared essentially as described in Examples 199 and 200 Method A:

Example #	Name	Starting material	^{1}H NMR ($CDCl_3$): δ	MS (found) (M+1)
201	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	6.72 (s, 1H), 3.36 (m, 1H), 3.19 (s, 6H), 2.57 (s, 3H), 2.51 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).	378
202	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethylamine	7.74 (s, 1H), 6.67 (s, 1H), 3.35 (m, 1H), 2.23 (s, 6H), 2.67(s, 3H), 2.61 (s, 3H), 1.84 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H).	344
203	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-methylamine	6.71 (s, 1H), 3.76 (t, J = 5.3 Hz, 2H), 3.71 (t, J = 5.1 Hz, 2H), 3.42 (s, 3H), 3.36 (m, 1H), 3.20 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 1.85 (m, 4H), 0.90 (t, J = 7.1 Hz, 6H).	423
204	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-(2-methoxy-ethyl)-	7.72 (s, 1H), 6.68 (s, 1H), 3.80 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.7 Hz, 2H), 3.42 (s, 3H), 3.35 (m, 1H), 3.26 (s, 3H), 2.67 (s, 3H), 2.61 (s, 3H), 1.84	388

	methylamine	methylamine	(m, 4H), 0.88 (t, J = 7.7 Hz, 6H).	
205	N-{4-Chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	6.71 (s, 1H), 4.48 (m, J = 7.4, 13.2 Hz, 1H), 3.34 (m, J = 7.6, 14.4 Hz, 1H), 3.04 (s, 3H), 2.76 (s, 3H), 2.61 (s, 3H), 1.85 (m, 4H), 1.31 (d, J = 7.1 Hz, 6H), 0.88 (t, J = 7.3 Hz, 6H).	407
206	N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-isopropyl-amine	N-{4-Bromo-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-N-methyl-i-propyl-amine	7.72 (s, 1H), 6.67 (s, 1H), 4.48 (m, 1H), 3.33 (m, 1H), 3.03 (s, 3H), 2.66 (s, 3H), 2.60 (s, 3H), 1.84 (m, 4H), 1.31 (d, J = 6.8, 6H), 0.88 (t, J = 7.2 Hz, 6H).	371

Example 207.

Preparation of N-{5-[7-chloro-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.

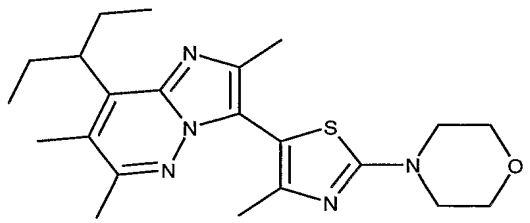


50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 2.0 ml of

dry DMF and 31 mg of CuCl (0.3 mmol) is added. The vial is capped with a Teflon® lined cap and heated at 120°C for overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 39.2 mg of the title compound. Yield 87%. mass spectrum (m/e): 435(M+1). 3.88 (t, J = 4.8 Hz, 4H), 3.57 (t, J = 5.1 Hz, 4H), 2.64(s, 3H), 2.44 (s, 3H), 2.18 (s, 3H), 2.00 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 208.

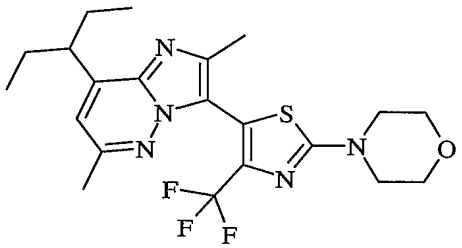
Preparation of N-{5-[7-bromo-8-(1-ethyl-propyl)-2,6,7-trimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine.



50 mg of N-{5-[7-Bromo-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methyl-thiazol-2-yl}-morpholine (0.1 mmol) is dissolved in 4 ml of Et2O and cooled to –78°C. 0.09 ml of n-BuLi 1.6M in hexane (0.15 mmol) is added at –78°C and stirred at –78°C for 20 min. 43 mg of iodomethane (0.3 mmol) is added to the mixture and stirred at –78°C and allowed to come to room temperature overnight. The reaction is quenched with sat. NH4Cl and extracted with Et2O. The separated organic layer is dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 29.6 mg of the title compound. Yield 69%. mass spectrum (m/e): 414(M+1). ^{1}H NMR ($CDCl_3$): δ 3.87 (t, J = 4.6 Hz, 4H), 3.56 (t, J = 4.6 Hz, 4H), 3.35 (m, 1H), 2.54 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.01 (m, 4H), 0.88 (m, 6H).

Example 209.

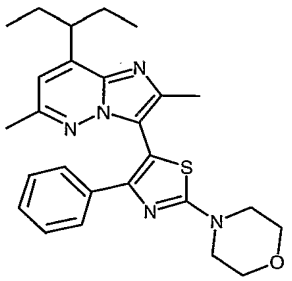
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-trifluoromethyl-thiazol-2-yl}-morpholine.



170 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.37 mmol) and 100 mg of sodium trifluoroacetate (0.74 mmol) are dissolved in 3 ml of DMF/toluene = 2/1. N2 gas is bubbled into the mixture for 20 min and 141 mg of CuI (0.74 mmol) is added. The vial is sealed and heated in the microwave at 210°C for 30 min. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1 and CH3CN : CH2Cl2 : Hexane = 5 : 45 : 50) to give 64.3 mg of the title compound. Yield 38%. mass spectrum (m/e): 454(M+1). ^{1}H NMR ($CDCl_3$): δ 6.72 (s, 1H), 3.88 (m, 4H), 3.60 (m, 4H), 3.32 (m, 1H), 2.54 (s, 3H), 2.47 (s, 3H), 1.85 (m, 4H), 0.89 (t, J = 7.0 Hz, 6H).

Example 210.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-phenyl-thiazol-2-yl}-morpholine.

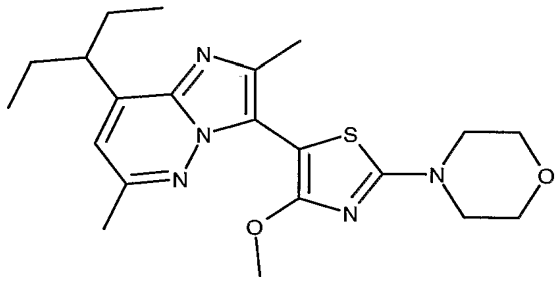


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 40 mg of phenylboronic acid (0.33 mmol) and 0.27 ml of 2 M Na2CO3aq.(0.55 mmol) are put in 2.5 ml of DME / water / EtOH = 7 / 3 / 1. N2 gas is bubbled in the mixture for 20 min and 20 mg of Pd(PPh3)4

(0.017 mmol) is added. The vial is sealed and heated at 160°C for 30 min in Microwave. The reaction mixture are added CH2Cl2 and water and the organic layer is separated, washed with brine, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane : AcOEt = 10:1) to give 27 mg of the title compound. Yield 54% mass spectrum (m/e): 462(M+1). δ 8.29(m, 1H), 7.60(m, 2H), 7.44(m, 1H), 7.22(m, 1H), 6.70 (s, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.64 (t, J = 5.0 Hz, 4H), 3.36 (m, 1H), 2.52 (s, 3H), 2.09 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 211.

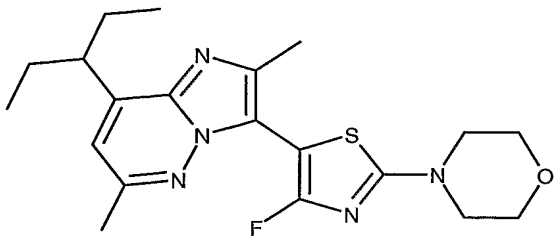
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-morpholine.



100 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol), 24 mg of sodium methoxide (0.44 mmol) and 21 mg of CuI (0.11 mmol) are put into 4 ml vial with MeOH 3 ml and capped with a Teflon® lined cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane : THF = 10 : 1) to give 32.8 mg of the title compound. Yield 36%. Mass spectrum (m/e): 416(M+1). ^{1}H NMR ($CDCl_3$): δ 6.64 (s, 1H), 3.96 (s, 3H), 3.86 (t, J = 4.7 Hz, 4H), 3.53 (m, 4H), 3.34 (m, 1H), 2.82 (s, 3H), 2.48 (s, 3H), 1.82 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H).

Example 212.

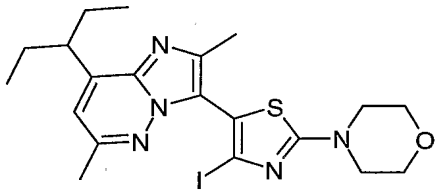
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-fluoro-thiazol-2-yl}-morpholine.



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol) is dissolved in 4 ml of diethylether and cooled to –78°C and 0.1 ml of n-BuLi 1.6M in hexane (0.16 mmol) is added at –78°C and stirred at –78°C for 20 min. 104 mg of N-fluorobenzene sulfonimide (0.33 mmol) in 2 ml of toluene is added at –78°C and stirred at room temperature for 1h. sat. NH4Cl is added, and the mixture is extracted with Et2O, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:AcOEt=3:1) to give 4.1 mg of the title compound. Yield 10%. Mass spectrum (m/e): 404 (M+1). 6.71 (s, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.55 (t, J = 5.0 Hz, 4H), 3.34 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 1.84 (m, 4H), 0.88 (t, J = 7.4 Hz, 6H).

Example 213.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-morpholine.

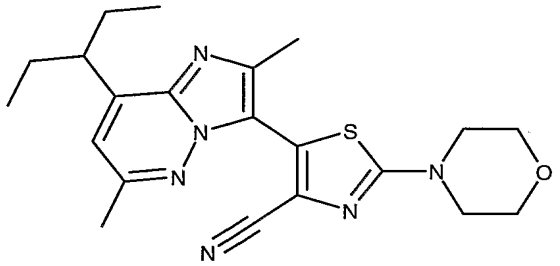


50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), 30 mg of CF_3CO_2Na (0.22 mmol) and 42 mg of CuI (0.22 mmol) are put into 4 ml vial with DMF / toluene = 2:1. The vial is capped with a Teflon cap and heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane :AcOEt = 5 : 1) to give 54 mg of the

title compound. 96%. Mass spectrum (m/e): 512 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 3.87 (t, J = 5.4 Hz, 4H), 3.58 (t, J = 5.4 Hz, 4H), 3.36 (m, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 1.85 (m, 4H), 0.91 (t, J = 5.4 Hz, 6H).

Example 214.

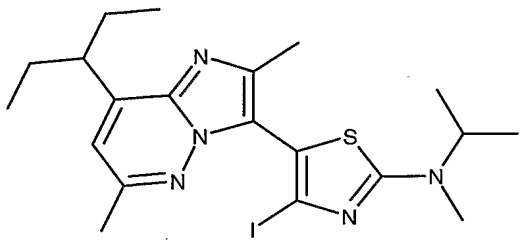
Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-2-morpholin-4-yl-thiazole-4-carbonitrile



50 mg of 3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.11 mmol), and 30 mg of CuCN (0.33 mmol) are put into 4 ml vial with 2 ml of DMF and the vial is capped with a Teflon cap. The vial is heated at 150°C overnight. The reaction mixture is applied onto a silica-gel chromatography column (Hexane:AcOEt=5:1) to give 12.3 mg of the title compound. Yield 28%. Mass spectrum (m/e): 411(M+1). 6.77 (s, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.61 (t, J = 5.0 Hz, 4H), 3.32 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.86 (m, 4H), 0.90 (t, J = 7.4 Hz, 6H).

Example 215.

Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-iodo-thiazol-2-yl}-N-isopropyl-methylamine.

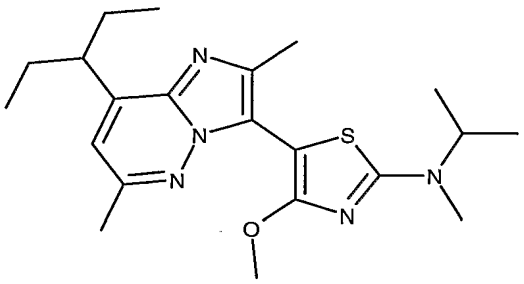


The title compound is prepared essentially as described in Example 213, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-

bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 17.9 mg. Yield 22%: mass spectrum (m/e):498 (M+1). ^{1}H NMR ($CDCl_3$): δ 6.71 (s, 1H), 4.41 (m, 1H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.53 (s, 3H), 1.84 (m, 4H), 1.29 (d, J = 5.8 Hz, 6H), 0.90 (t, J = 7.2 Hz, 6H).

Example 216.

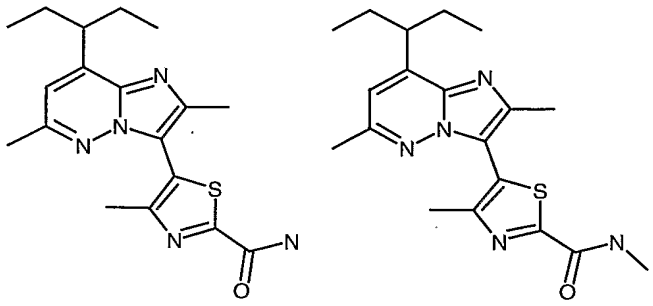
Preparation of N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-methoxy-thiazol-2-yl}-N-isopropyl-methylamine.



The title compound is prepared essentially as described in Example 211, employing N-{5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]- 4-bromo-thiazol-2-yl}-N-isopropyl-methylamine to give 52.7. Yield 36%: mass spectrum (m/e):402(M+1). ^{1}H NMR ($CDCl_3$): δ 6.63 (s, 1H), 4.44 (m, 1H), 3.96 (s, 3H), 3.35 (m, 1H), 2.97 (s, 3H), 2.57 (s, 3H), 2.50 (s, 3H), 1.83 (m, 4H), 1.29 (d, J = 6.7 Hz, 6H), 0.88 (t, J = 8 Hz, 6H).

Example 217 and 218.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide and 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid N-methylamide.



217. 218.

180 mg of 8-(1-Ethyl-propyl)-3-[2-bromo-4-methyl-5-thiazolyl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.46 mmol) and 124 mg of copper(I) cyanide are put into 4 ml vial with 2 ml of dry DMF. The vial is closed with a Teflon can and heated at 130°C overnight. The crude reaction mixture is applied onto a silica-gel chromatography column (Hexane : AcOEt = 1:1 →1:3) to give

52.1 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (32%) and

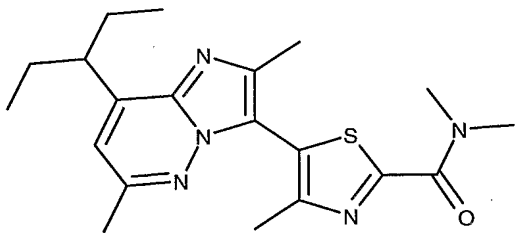
7.6 mg of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide.

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide: mass spectrum (m/e): 358(M+1) ^{1}H NMR ($CDCl_3$): δ 7.21 (s, NH), 6.76 (s, 1H), 5.59 (s, NH), 3.34 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.42 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H). and

5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid methylamide: mass spectrum (m/e): 372(M+1). ^{1}H NMR ($CDCl_3$): 8.77 (s, NH), 6.75 (s, 1H), 4.06 (s, 3H), 3.35 (m, 1H), 2.55 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 1.87 (m, 4H), 0.91 (t, J = 7.6 Hz, 6H).

Example 219.

Preparation of 5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid dimethylamide.

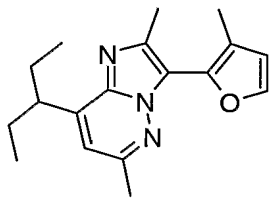


5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazole-2-carboxylic acid amide (46 mg, 0.13 mmol) and 28 mg of sodium *tert*-Butoxide (0.30 mmol) are put into 4 ml of dry DMSO and stirred at room temperature for 5 min. 141 mg of iodomethane (1.0 mmol) is added and stirred at room temperature for 1 h.

Water is added, and the mixture is extracted with CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane :AcOEt=3:1) to give 22.3 mg of the title compound. Yield 45%: mass spectrum (m/e):386(M+1). 6.75 (s, 1H), 3.70 (s, 3H), 3.35 (m, 1H), 3.21 (s, 3H), 2.55 (s, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.86 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H).

Example 220.

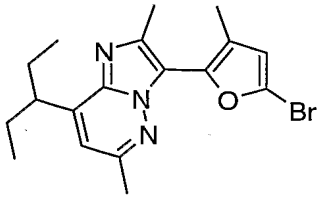
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 3-methylfuran (Acros, 232 mg, 2.83 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 1.8 mL, 2.9 mmol). After addition of the nBuLi, the solution is warmed to 0 °C for 15 minutes, then to room temperature for an additional 5 minutes. The reaction mixture is then cooled to -78 °C and treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 5.8 mL, 2.9 mmol). The resulting mixture is warmed to room temperature and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (400 mg, 1.17 mmol) and $PdCl_2(dppf) - CH_2Cl_2$ complex (Aldrich, 95 mg, 0.12 mmol). The mixture is heated to 60 °C for 4 hours, then poured into 1 N HCl (60 mL) and extracted with ethyl acetate (2x60 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound as an oil pyridazine (149 mg, 43% yield). ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.5 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.59 (d, J = 1.8 Hz, 1H), 6.71 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 3.36 (m, 1H), 2.55 (s, 3H), 2.50 (s, 3H), 2.10 (s, 3H), 1.92-1.79 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H).

Example 221.

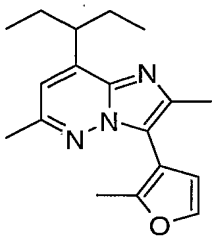
Preparation of 3-(5-bromo-3-methyl-furan-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (4 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-furan-2-yl)-imidazo[*1,2-b*]pyridazine (32.4 mg, 0.11 mmol) is cooled to 0 °C under a $CaSO_4$ drying tube and treated with NBS (20.1 mg, 0.11 mmol). After 15 minutes at 0 °C, the mixture is warmed to room temperature. After an additional 10 minutes, the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (26.3 mg, 64% yield) as a solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 3.34 (m, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 2.07 (s, 3H), 1.93-1.77 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H).

Example 222.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A. 3-Bromo-2-methyl furan.

A THF solution (10 mL) of 2,3-dibromofuran (Lancaster, 5.54 gm, 24.5 mmol) under N_2 is treated with $PdCl_2(PPh_3)_2$ (860 mg, 1.2 mmol) and stirred for 10 minutes at

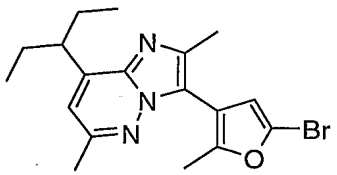
room temperature. The solution is then treated with CH_3ZnCl (Aldrich, 2.0 M in THF, 15 mL, 30 mmol). The resulting mixture is stirred at room temperature overnight then poured into 1 N HCl and extracted into diethyl ether. The organic extract is washed with sat. NaCl, dried over Na_2SO_4, and filtered. The filtrate is then distilled and the product is collected at 120-125 °C to give the title compound as a colorless oil (1.71 gm, 43% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 7.25 (d, J = 1.8 Hz, 1H), 6.34 (d, J = 1.8 Hz, 1H), 2.28 (s, 3H).

B. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.

A THF solution (10 mL) of 3-bromo-2-methyl furan (prepared as described above) (1.06 gm, 6.58 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 4.1 mL, 6.6 mmol). After 10 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 13.2 mL, 6.6 mmol). The resulting mixture is warmed to room temperature then treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.13 gm, 3.29 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 257 mg, 0.31 mmol). The mixture is heated to 60 °C for 4 hours, then poured into sat. NH_4Cl (50 mL) and extracted with diethyl ether (2x50 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (685 mg, 70% yield) as an oil. ES-MS (m/z): calc'd for $C_{18}H_{23}N_3O$: 297.2; found 298.2 (M+H); ^1H NMR (400 mHz, $CDCl_3$): δ 7.45 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.60 (d, J = 2.0 Hz, 1H), 3.35-3.31 (m, 1H), 2.51 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H), 1.88-1.75 (m, 4H), 0.86 (t, J = 7.5 Hz, 6H).

Example 223.

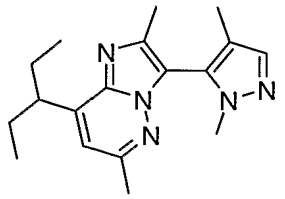
Preparation of 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A CH_2Cl_2 solution (2 mL) of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-furan-3-yl)-imidazo[*1,2-b*]pyridazine (42.3 mg, 0.14 mmol) under a $CaSO_4$ drying tube is treated with N-bromosuccinimide (27.6 mg, 0.16 mg). After 30 minutes the reaction mixture is poured into H_2O (25 mL) and extracted into CH_2Cl_2 (2x25 mL). The combined organic extracts are washed with sat. NaCl, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 12% ethyl acetate in hexane) to elute the title product (36.9 mg, 70% yield) as a white solid. ES-MS (m/z): calc'd for $C_{18}H_{22}BrN_3O$: 375.1; found 376.3 (M+H); ^{1}H NMR (400 mHz, $CDCl_3$): δ 6.67 (s, 1H), 6.50 (s, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 1.90-1.73 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H).

Example 224.

Preparation of 3-(2,4-dimethyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

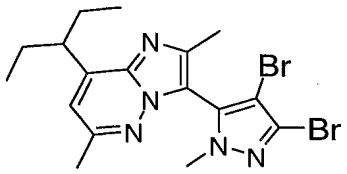


n-BuLi (1.3 ml, 2.09 mmol) is stirred in THF (4 ml), under N_2, and cooled to –72^{0}C. 1,4-dimethyl-*1H*-pyrazole (170 mg, 2.04 mmol, in THF, 1 ml) is added slowly, stirred for 5 min. then allowed to warm to ambient temp. and stirred for 45 min. The mixture is cooled to –72°C and a zinc chloride solution (4.3 ml, 2.14 mmol, 0.5 M in toluene) added, warmed to ambient temp. and treated with 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 40 mg, 0.05 mmol). The mixture is heated to 65^{0}C overnight, cooled to ambient temp., added to water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50 % ethyl acetate in hexane) to elute the product. The title compound is obtained (0.7% yield). ES-MS (m/z): calc'd for $C_{18}H_{25}N_5$: 311.4; found 312.2 $(M+H)^+$. ^{1}H NMR (400 mHz, $CDCl_3$):

δ 7.51 (s, 1H), 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.53 (s, 3H), 2.43 (s, 3H), 2.00 (s, 3H), 1.87 (m, 4H), 0.92 (m, 6H)..

Example 225.

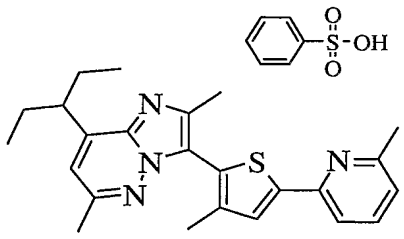
Preparation of 3-(4,5-dibromo-2-methyl-*2H*-pyrazol-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.4 mmol), 3,4,5-tribromo-1-methyl-^{1}H-pyrazole (700 mg, 2.1 mmol) and cesium carbonate (900 mg, 2.8 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (14 mg) is added and the mixture heated to 130°C overnight. The mixture is added to water and extracted twice with EtOAc. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title product (204 mg, 32% yield). ES-MS (m/z): calc'd for $C_{17}H_{21}Br_2N_5$: 455.2; found 455.9 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.75 (s, 1H), 3.72 (s, 3H), 3.33 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H), 1.84 (m, 4H), 0.88 (t, 6H).

Example 226.

Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine benzenesulfonic acid.

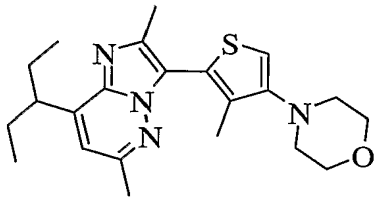


To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine (0.23 g, 0.57 mmol) and MeOH (1

mL) is added a solution of benzenesulfonic acid (0.096 g, 0.57 mmol) and MeOH (1 mL). The solution is concentrated to furnish the title compound (0.32 g, 0.57 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.0 Hz, 6H), 1.59-1.82 (m, 4H), 2.06 (s, 3H), 2.61 (s, 6H), 2.88 (s, 3H), 3.22-3.32 (m, 1H), 6.79 (bs, 2H), 7.25 (s, 1H), 7.33-7.42 (m, 3H), 7.49 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.4 Hz, 2H), 7.92 (dd, J = 7.4, 1.6 Hz, 1H) 8.23 (s, 1H). LC/MS (m/z): calcd. for $C_{24}H_{28}N_4S$ $(M+H)^+$: 405.2; found: 405.4.

Example 227.

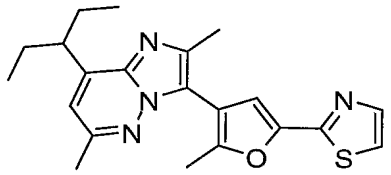
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-4-morpholin-4-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine.



To a flask containing 3-(4-bromo-3-methyl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30g, 0.76 mmol), morpholine (0.10 mL, 1.15 mmol), $Pd_2(dba)_3$ (0.035 g, 0.038 mmol), and 2-dicyclohexylphosphino-biphenyl-2'-(N,N-dimethyl-amino)biphenyl (0.018 g, 0.046 mmol) is added 1 M LiHMDS (1.9 mL, 1.91 mmol). The solution is heated at 65 °C overnight, diluted with EtOAc (30 mL), washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient), dissolved in Et_2O (20 mL) and extracted with 1 M HCl (2 x 30 mL). The aqueous layer is washed with Et_2O (20 mL), made basic with 5 M NaOH (15 mL), extracted with EtOAc (2 x 20 mL), the combined organic layers washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.047 g, 0.12 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.91 (m, 4H), 2.01 (s, 3H), 2.45 (s, 3H), 2.49 (s, 3H), 2.99-3.05 (m, 4H), 3.28-3.37 (m, 1H), 3.84-3.88 (m, 4H), 6.65 (s, 1H), 6.71 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{30}N_4OS$ $(M+H)^+$: 399.2; found: 399.2.

Example 228.

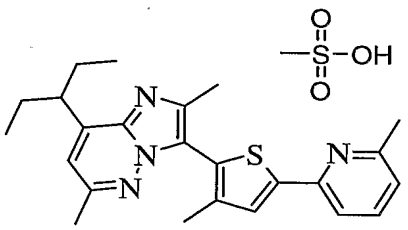
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(2-methyl-5-thiazol-2-yl-furan-3-yl)-imidazo[*1,2-b*]pyridazine.



A THF solution (5 mL) of 2-bromothiazole (Aldrich, freshly distilled, 75.0 μL, 0.84 mmol) is cooled to -78 °C under N_2 then treated with nBuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol). After 15 minutes at -78 °C, the mixture is treated with $ZnCl_2$ (Aldrich, 0.5 M in THF, 1.8 mL, 0.90 mmol). The resulting mixture is warmed to room temperature then treated with a THF slurry (1 mL) containing 3-(5-bromo-2-methyl-furan-3-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (60.1 mg, 0.16 mmol) and $PdCl_2$(dppf) – CH_2Cl_2 complex (Aldrich, 22 mg, 0.027 mmol). The mixture is heated overnight at 60 °C, then poured into sat'd NH_4Cl and extracted with diethyl ether. The organic extract is washed with aq. brine, dried over Na_2SO_4, filtered, and concentrated. The crude product is purified by chromatography using hexane-ethyl acetate gradient (100% hexane to 20% ethyl acetate in hexane) to elute the title compound (45.8 mg, 75% yield) as an oil. ES-MS (m/z): calc'd for $C_{21}H_{24}N_4OS$: 380.17; found 381.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.83 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 3.1 Hz, 1H), 7.20 (s, 1H), 6.68 (br s, 1H), 3.35 (br s, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.40 (s, 3H), 1.90-1.76 (m, 4H), 0.88 (t, J = 7.5 Hz, 6H).

Example 229.

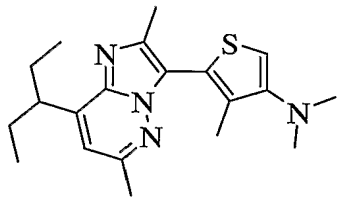
Preparation of 8-(1-ethyl-propyl)-2,6-dimethyl-3-[3-methyl-5-(6-methyl-pyridin-2-yl)-thiophen-2-yl]-imidazo[*1,2-b*]pyridazine; compound with methanesulfonic acid.



To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(3-methyl-5-pyridin-2-yl-thiophen-2-yl)-imidazo[*1,2-b*]pyridazine (0.55 g, 1.36 mmol) and MeOH (6 mL) is added methane sulfonic acid (0.088 mL, 1.36 mmol). After one hour the solution is concentrated and the solution is treated with Darco-60® for 1 hour, filtered and concentrated to furnish the title compound (0.68 g, 1.36 mmol, >99%). ^{1}H NMR ($CDCl_3$: CD_3OD 95:5) δ 0.85 (t, J = 7.4 Hz, 6H), 1.67-1.91 (m, 4H), 1.96 (s, 3H), 1.97 (s, 3H), 2.20 (s, 3H), 2.61 (s, 3H), 2.90 (s, 3H), 3.17-3.29 (m, 1H), 7.33 (s, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 8.34 (t, J = 7.9 Hz, 1H), 9.95 (bs, 1H). LC/MS (m/z): calcd. for $C_{25}H_{32}N_4O_2S_2$ $(M+H)^+$: 405.6; found: 405.6.

Example 230.

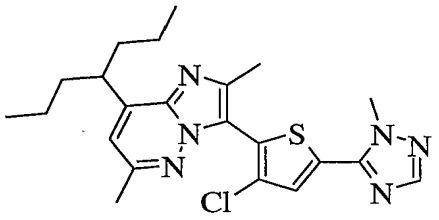
Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiophen-3-yl}-dimethyl-amine.



To a –78 °C solution of dimethyl-(4-methyl-thiophen-3-yl)-amine (0.43 g, 3.06 mmol) and THF (5 mL) is added 1.6 M *n*-BuLi (1.91 mL, 3.06 mmol). The solution is stirred for 1 hour, then 0.5 M $ZnCl_2$ (6.1 mL, 3.06 mmol) is added and the solution warmed to ambient temperature. After 30 minutes 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.70 g, 2.04 mmol) and $PdCl_2$(dppf) (0.075 g, 0.10 mmol) is added and the solution heated at 65 °C overnight. The solution is diluted with EtOAc (35 mL), washed with sat. NH_4Cl (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (15% -30% EtOAc gradient) furnish the title compound (0.13 g, 0.36 mmol, 18%). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.72-1.90 (m, 4H), 2.03 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 2.77 (s, 6H), 3.28-3.37 (m, 1H), 6.63 (s, 1H), 6.65 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{28}N_4S$ $(M+H)^+$: 357.2; found: 357.2

Example 231.

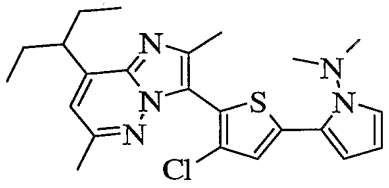
Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine.



A slurry of 2,6-dimethyl-8-(1-propyl-butyl)-imidazo[*1,2-b*]pyridazine (below) (0.30 g, 1.22 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-[1,2,4]triazole (below) (0.41 g, 1.47 mmol), KOAc (0.60 g, 6.11 mmol), TBABr (0.39 g, 1.22 mmol), and NMP (3 mL) is de-gassed with N_2 for 30 minutes. $Pd(OAc)_2$ (0.014 g, 0.061 mmol) and TDBPP (0.040 g, 0.061 mmol) are added and the solution heated at 125 °C for 2.5 hours. The solution is diluted with EtOAc (50 mL), washed with water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-40% EtOAc gradient) furnish the title compound (0.30 g, 0.68 mmol, 56%). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 6H), 1.14-1.39 (m, 4H), 1.76 (q, J = 16.3, 7.7 Hz, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.41-3.50 (m, 1H), 4.15 (s, 3H), 6.73 (s, 1H), 7.48 (s, 1H), 7.90 (s, 1H). LC/MS (m/z): calcd. for $C_{22}H_{27}ClN_6S$ $(M+H)^+$: 443.2; found: 443.3.

Example 232.

Preparation of (2-{4-chloro-5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiophen-2-yl}-pyrrol-1-yl)-dimethyl-amine.

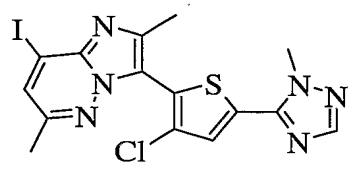


Using a procedure analogous to Example 27, 1-(dimethylamino)-pyrrole (0.20 mL, 1.65 mmol), THF (4 mL), 1.6 M *n*-BuLi (1.10 mL, 1.73 mmol), 0.5 M $ZnCl_2$ (3.46 mL, 1.73 mmol), 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.34 g, 0.82 mmol) and $PdCl_2$(dppf) (0.030 g, 0.041 mmol),

furnish the title compound (0.17 g, 0.38 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.52 (s, 6H), 2.84 (s, 6H), 3.28-3.39 (m, 1H), 6.21 (dd, J = 4.1, 3.2 Hz, 1H), 6.38 (dd, J = 4.1, 1.8 Hz, 1H), 6.68 (s, 1H), 7.02 (dd, J = 3.2, 1.8 Hz, 1H), 7.29 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{28}ClN_5S$ $(M+H)^+$: 442.2; found: 442.3.

Example 233.

Preparation of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Chloro-thiophene-2-carbonitrile.

A 22-L reaction flask is equipped with a cooling bath, air stirrer, gas addition tube, and thermometer probe. The flask is purged with nitrogen, then charged $AlCl_3$ (1025 g, 7.69 moles) and $CHCl_3$(6.6 L, 16.5 vol.). After cooling the mixture to 0-5 °C, it is charged with 2-thiophene carbonitrile (400 g, 3.66 moles) dropwise via an addition funnel over 10-15 minutes while maintaining the temperature at ≤ 10 °C. The mixture is charged with Cl_2 gas (300g, 4.23 moles, 1.16 EQ) subsurface at ≤ 10 °C over 1.25 hours. The progress of the reaction is monitored by GC, wherein the GC sampling method is quenching an aliquot of the reaction mixture into 6N HCl, extracting with EtOAc, drying over Na_2SO_4, filtering, and injecting the filtrate.

When the reaction is deemed complete by GC analysis [the reaction was deemed complete when the ratio of (sm : prod : dichloro) was approximately (1 : 5.8 : 1) by area % GC.], 6N HCl (8.0 L) is added dropwise via addition funnel over 1.5 hours, while maintaining the temperature at ≤ 20 °C [The HCl addition is extremely exothermic and evolves gas]. The reaction is transferred to a separatory funnel and the layers are separated. After extracting the aqueous layer with $CHCl_3$ (4.0 L), the chloroform layers are combined and washed with de-ionized H_2O (6.0L). The organic layer is dried over Na_2SO_4, filtered and concentrated under vacuum to give a pale yellow semi solid 575g, 109.3%). GC (60°C to 280°C temperature gradient) Area-% analysis shows ~68%

product (t_{ret} = 6.5 min) with major impurities being the unreacted starting material (t_{ret} = 5.1 min) and the dichlorinated product (t_{ret} = 7.4 min). GC Method: Column: DB1; $T_{injecyt}$ = 300 °C ; $T_{initial}$ = 60 °C, t = 2.0 min; T_{final} = 280 °C, rate = 18 °C/min.

B. 4-Chloro-2-thiophene carboxamide.

A 12-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with KOH (288.6 g, 5.143 moles) and De-ionized H_2O (6.04 L) to form a solution that exotherms to ~31 °C. After allowing the solution to cool to ~28.0 °C, th mixture is charged with 4-chloro-2-thiophene carbonitrile (671.3 g, 4.675 moles)[1] followed by EtOH (675 mL). A gradual exotherm occurs upon the addition of EtOH and continues over 1-1.5 hours to ~38 °C. The reaction is stirred at ambient temperature overnight.

The reaction mixture is filtered under vacuum, washed with de-ionized H_2O and dried to give crude product. The solids are dissolved in EtOAc (10.0 L) treated with Na_2SO_4 and Darco for 1-2 hours; then, filtered and washed with EtOAc. The filtrate is concentrated on the Büchi until solids began to precipitate out at 45 °C at which time the vacuum is released, and the temperature is increased to 60-65 °C to redissolve the solids. With stirring at 60 °C, heptane (3.5 L) is added slowly to precipitate solids. After stirring for 15-20 minutes at 60 °C, the mixture is cooled to 30-40 °C and filtered. The solids are washed with heptane (2 x 0.75 L), and dried to give the title compound (t_{ret} = 9.9 min) as a white solid (235.4 g, 31.2 % 96.4 area % by GC analysis). A second crop is obtained from the filtrate to give 67.8 g, 9.0 %; 94.5% area-% by GC analysis). The Overall yield is 303.2 g, 40.1 %.

C. 4-Chloro-N-dimethylaminomethylene-2-thiophene carboxamide.

A 5-L reaction flask equipped with a heating mantle, air stirrer, Dean-Stark apparatus, and thermometer probe is charged with 4-chloro-2-thiophene carboxamide. (300 g, 1.856 moles) and dimethylformamide dimethylacetal (872 mL) to form a slurry that endotherms 1-2 °C from 22-20 °C. The mixture is heated gradually to 96 °C while collecting the distillate (mostly MeOH). The heating mantle is removed, and the mixture is cooled to $\leq$ 25 °C. De-ionized H_2O (3.0 L) is added via an addition funnel and the

[1] A small amount of solids were undissolved at this point.

temperature is maintained at $\leq$35 °C. The reaction mixture is extracted with EtOAc (1 x 3.0 L, 1 x 1.5 L), then combined the organics are washed with de-ionized H_2O (1.5 L). The organic phase is dried over Na_2SO_4, filtered, and concentrated under vacuum to give crude product (400 g).

The crude product is dissolved in EtOAc (320 mL, 0.8 Vol) at 50-60 °C; then, heptane (1700 mL, 4.25 Vol) is added slowly while gradually increasing the temperature to 70 °C. A seed crystal (Lot: PP6-H00086-075-1) is added to the cloudy solution to initiate precipitation. The resulting mixture is stirred to room temperature overnight, then filtered and washed with heptane. The solids are dried to give the title compound (t_{ret} = 13.0 min) as a white solid (329.8 g, 82%; 98.2 % area-% by GC analysis).

D. 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide. (155 g, 0.715 moles) and HOAc (1500 mL) to form a solution. Using an ice-water cooling bath to maintain the temperature at $\leq$ 30 °C, methylhydrazine (33.2 g, 0.721 moles) is added dropwise via an addition funnel over 15-20 minutes to form a light yellow slurry. Gradually, the reaction is heated to 90 °C and held at 90 °C for 30 minutes. After analysis of the mixture by GC, the reaction is cooled to ~70 °C; then, concentrated to a thick oil/slurry. De-ionized H_2O (1.67 L) is slowly added to precipitate solids; then, the mixture is cooled to < 30 °C, filtered and washed with de-ionized H_2O (1.67 L). The wet solids (125.8 g) are re-dissolved in warm MTBE (1.64 L), dried over Na_2SO_4, filtered and concentrated to dryness giving the title compound as a pale yellow solid (85.8 g, 60.1% 91.9 % area % by GC).

E. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole.

A 3-L reaction flask equipped with a cooling bath, air stirrer, and thermometer probe is charged with 5-(4-Chloro-thiophen-2-yl)-1-methyl-^{1}H-[1,2,4]triazole (105.3 g, 0.527 moles), ACN (1053 mL) and HOAc (105 mL) to form a solution. NBS

(103.2 g, 0.580 moles) is added portion-wise over 30-60 minutes while maintaining the temperature at ≤ 31 °C. After stirring for 1 hour[2], GC analysis indicated reaction completion. The reaction mixture is poured into de-ionized H_2O (2.1 L, 20vol), stirred for 30 minutes, filtered, and washed with de-ionized H_2O (2 x 1 L). The product is dried in a vacuum oven at 45 °C overnight to give the title compound as a pale yellow solid (123.0 g, 83.8 %; 96.6 % area-% by GC).

F. 2,6-Dimethyl-imidazo[1,2-*b*]pyridazine.

A 3 neck 1L round bottom flask is charged with 6-methyl-pyridazin-3-ylamine (20 g, 0.18 moles), ethanol 2B (200 mL), and chloroacetone (23.7 g, 20.4 mL, 0.256 moles, 1.4 equiv). The reaction mixture is heated at 70 °C overnight. NaHCO3 (23.2 g, 0.276 moles, 1.5 equiv) is added portion wise. After most of bubbling subsides, the reaction is heated at 100 °C overnight. The solvents are removed in vacuo and the residue is taken up in dichloromethane and filtered through a filter paper. The solvent is again removed in vacuo. The residue is purified using silica gel chromatography with a hexanes:ethyl acetate gradient to obtain the title compound (15.5 g, 57%). ^{1}H-NMR (DMSO-d6), δ 2.34 (s, 3H), 2.47 (s, 3H), 7.03, (d, J = 10 Hz, 1H), 7.85 (d, J = 10 Hz, 1H), 7.91 (s, 1H) ppm. MS (APCI): 148 (M+1).

G. 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.32 g, 2..17 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^{1}*H*-[1,2,4]triazole (0.72 g, 2.61 mmol), Cs_2CO_3 (1.49 g, 4.57 mmol) and DMF (6 mL) is de-gassed for 15 minutes with N_2. $Pd(OAc)_2$ (0.024 g, 0.11 mmol) and PPh_3 (0.057 g, 0.22 mmol) are added and the solution is heated at 135°C for 4 hours. The solution is diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (2 x 50 mL), water (50 mL), filtered and concentrated. The residue is purified by ISCO flash chromatography (30%-100% EtOAc gradient) furnish the title compound (0.29 g, 0.84 mmol, 39%). ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.50 (s, 3H), 4.10 (s, 3H), 6.92 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H). LC/MS (m/z): calcd. for $C_{15}H_{13}ClN_6S$ $(M+H)^+$: 345.1; found: 345.2.

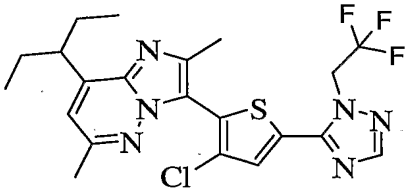
[2] The reaction temperature decreased after 1 hour to 26.7 °C

H. 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a –78 °C solution of 3-[3-chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.50 g, 4.35 mmol) and THF (50 mL) is added I_2 (1.21 g, 4.78 mmol). After 10 minutes 2 M LDA (5.44 mL, 10.87 mmol) is added. The solution is stirred for 30 minutes, quenched with water, diluted with EtOAc (100 mL), washed with water (100 mL), sat. $Na_2S_2O_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (100% EtOAc) furnish the title compound (0.61 g, 1.30 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.55 (s, 3H), 4.14 (s, 3H), 7.47 (s, 1H), 7.51 (s, 1H), 7.89 (s, 1H),. LC/MS (m/z): calcd. for $C_{15}H_{12}ClIN_6S$ $(M+H)^+$: 471.0; found: 471.0.

Example 234.

Preparation of 3-{3-chloro-5-[2-(2,2,2-trifluoro-ethyl)-2*H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 5-(4-Chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

To a solution of 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (1.00 g, 4.62 mmol) and AcOH (1. mL) is added 70 % aqueous 2,2,2-trifluoroethyl-hydrazine (0.79 mL, 4.85 mmol). The solution is heated at 90 °C for 45 minutes, concentrated, dissolved in Et_2O (40 mL), washed with water (30 mL), sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (1.24 g, 4.62 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.8, 7.8 Hz, 2H), 7.28 (d, J = 0.9 Hz, 1H), 7.31-7.33 (m, 1H), 7.94 (s, 1H). LC/MS (m/z): calcd. for $C_8H_5ClF_3N_3S$ $(M+H)^+$: 268.0; found: 268.0.

B. 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-^{1}*H*-[1,2,4]triazole.

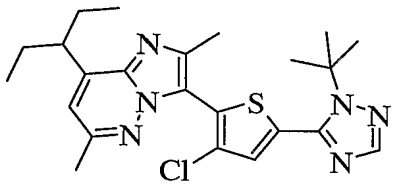
To a solution of 5-(4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (1.13 g, 4.22 mmol) and AcOH (10 mL) in a sealed tube, is added Br_2 (0.23 mL, 4.43 mmol). The solution is heated at 120 °C for 2 hours, and 140 °C for 5 hours. The solution is concentrated, diluted with Et_2O (150 mL), washed with sat $NaHCO_3$ (75 mL), sat. $Na_2S_2O_3$ (75 mL), brine (75 mL) dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (5%-15% EtOAc gradient) furnish the title compound (1.04 g, 3.00 mmol, 71%). ^{1}H NMR ($CDCl_3$) δ 4.88 (q, J = 16.0, 7.9 Hz, 2H), 7.22 (s, 1H), 7.99 (s, 1H). LC/MS (m/z): calcd. for $C_8H_4BrClF_3N_3S$ $(M+H)^+$: 345.9; found: 346.0.

C. 3-{3-Chloro-5-[2-(2,2,2-trifluoro-ethyl)-*2H*-[1,2,4]triazol-3-yl]-thiophen-2-yl}-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.25 g, 1.14 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.47 g, 1.37 mmol), KOAc (0.56 g, 5.60 mmol), TBABr (0.37 g, 1.14 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and TDBPP (0.037 g, 0.057 mmol) furnish the title compound (0.43 g, 0.89 mmol, 78%). ^{1}H NMR ($CDCl_3$), δ 0.88 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.52 (s, 3H), 2.53 (s, 3H), 3.27-3.36 (m, 1H), 4.98 (q, J = 15.7, 7.9 Hz, 2H), 6.74 (s, 1H), 7.45 (s, 1H), 8.03 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{22}ClF_3N_6S$ $(M+H)^+$: 483.1; found: 483.2.

Example 235.

Preparation of 3-[5-(2-tert-butyl-*2H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-*tert*-Butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole.

Using a procedure analogous to Example 234A, 4-chloro-N-dimethylaminomethylene-2-thiophene carboxamide (5.00 g, 23.07 mmol) and AcOH (50.

mL), *tert*-butylhydrazine hydrochloride (3.16 g, 25.38 mmol) furnish the title compound (0.20 g, 0.83 mmol, 3.6%). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9H), 7.07 (d, J = 1.3 Hz, 1H), 7.51 (d, J = 1.3 Hz,1H), 8.08 (s, 1H).

B. 5-(5-Bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole.

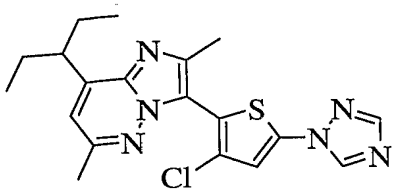
Using a procedure analogous to Example 249B, 1-*tert*-butyl-5-(4-chloro-thiophen-2-yl)-*1H*-[1,2,4]triazole (0.20 g, 0.83 mmol), AcOH (3 mL) and Br_2 (0.051 mL, 0.99 mmol) furnish the title compound (0.27 g, 0.83 mmol, >99%). ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9H), 7.42 (s, 1H), 8.08 (s, 1H). LC/MS (m/z): calcd. for $C_{10}H_{11}BrClN_3S$ $(M+H)^+$: 320.0; found: 320.0.

C. 3-[5-(2-tert-Butyl-*2H*-[1,2,4]triazol-3-yl)-3-chloro-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using a procedure analogous to Example 231, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 g, 0.68 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-(2,2,2-trifluoro-ethyl)-*1H*-[1,2,4]triazole (0.20 g, 0.82 mmol), KOAc (0.34 g, 3.42 mmol), TBABr (0.22 g, 0.68 mmol), and NMP (3 mL), $Pd(OAc)_2$ (0.0077 g, 0.034 mmol) and TDBPP (0.022 g, 0.034 mmol) furnish the title compound (0.039 g, 0.085 mmol, 13%). ^{1}H NMR ($CDCl_3$), δ 0.87 (t, J = 7.5 Hz, 6H), 1.65 (s, 9H), 1.73-1.91 (m, 4H), 2.51 (s, 6H), 3.26-3.37 (m, 1H), 6.69 (s, 1H), 7.65 (s, 1H), 8.11 (s, 1H). LC/MS (m/z): calcd. for $C_{23}H_{29}ClN_6S$ $(M+H)^+$: 457.2; found: 457.3.

Example 236.

Preparation of 3-(3-chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 3-(3-Chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

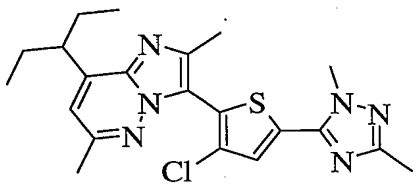
To a solution of 3-(3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine (2 g, 6 mmol) in 10 mL of anhydrous CH_3CN under nitrogen was added portionwise NIS (1.6 g, 7.2 mmol). The reaction mixture is stirred at reflux for 14 hours. After cooling, the solvent is concentrated under vacuum, the residue is disolved in EtOAc and washed with H_2O, 5% solution of sodium bisulfite, H_2O and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under vacuum. The crude residue is purified by silica gel chromatography using hex/EtOAc 8:2 as eluent mixture, to obtain 2.4 g (90%) of the title compound; mass spectrum 460 (M+1); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.71 (s, 1H), 3.32 (q, 1H, J = 7.2 Hz), 2.52 (s, 3H), 2.49 (s, 3H), 1.84 (q, 4H, J = 7.2 Hz); 0.88 (t, 6H, J = 7.2 Hz) ppm.

B. 3-(3-Chloro-5-[1,2,4]triazol-1-yl-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(3-chloro-5-iodo-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.65 mmol), *1H*-triazole (0.047 g, 0.69 mmol), CuI (0.0062, 0.033 mmol), Cs_2CO_3 (0.45 g, 1.37 mmol) and DMF (3 mL) is added (*1S, 2S*)-(+)-*N,N'*- dimethylcyclohexane-1,2-diamine (0.014 mL, 0.098 mmol). The solution is heated at 112 °C overnight, diluted with CH_2Cl_2 (10 mL) and filtered thru Celite® and concentrated. The residue is purified by ISCO flash chromatography (30%-40% EtOAc gradient furnish the title compound (0.028 g, 0.070 mmol, 11%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.75-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.35 (m, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 8.10 (s, 1H), 8.50 (s, 1H). LC/MS (m/z): calcd. for $C_{19}H_{21}ClN_6S$ $(M+H)^+$: 401.1; found: 401.2.

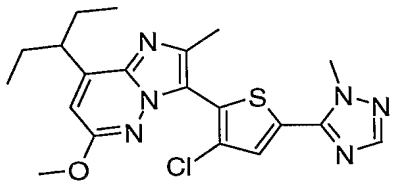
Example 237.

Preparation of 3-[3-chloro-5-(2,5-dimethyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.30 g, 0.72 mmol) and THF (5 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 15 minutes MeI (0.052 mL, 0.83 mmol) is added and the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The solution is recrystalized from acetone: hexane furnish the title compound (0.13 g, 0.30 mmol, 42%). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.36 (s, 3H), 2.51 (s, 6H), 3.27-3.39(m, 1H), 3.40 (s, 3H), 6.72 (s, 1H), 8.02 (s, 1H). LC/MS (m/z): calcd. for $C_{21}H_{25}ClN_6S$ $(M+H)^+$: 429.2; found: 429.2.

Example 238.Preparation of 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. N-(6-Methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide.

3-Chloro-6-methoxy-pyridazine (10.0 g, 69. 18 mmol) is mixed with 2,2-dimethyl-propionamide (8.40 g, 83.01 mmol), BINAP (2.15 g, 3.46 mmol), Cs_2CO_3 (33.8 g, 103.77 mmol) in 1,4-dioxane (150 mL). It is degassed by passing N_2 through for 10 min at rt. $Pd_2(dba)_3$ (3.16 g, 3.46 mmol) is added and the resulting mixture is refluxed overnight. The mixture is cooled to rt, diluted with EtoAc (150 mL); filtered through silica gel; washed with EtOAc (2 x 150 mL). The filtrate is washed with H2O (2 x 300 mL); dried with $MgSO_4$; filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (6.59 g, 31.53 mmol, 46%). 1H NMR (CDCl3): δ. 1.35 (s, 9H), 4.08 (s, 3H), 7.01 (d, J = 9.7 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.44 (bs, 1H). ES-MS (m/z): calcd for $C_{10}H_{15}N_3O_2$ $(M+H)^+$: 210.3; found : 210.1.

B. N-[4-(1-Ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide.

Using a procedure analogous to Example 6a, from N-(6-methoxy-pyridazin-3-yl)-2,2-dimethyl-propionamide (6.09 g, 29.14 mmol) and a Grignard reagent prepared from 3-pentyl bromide (18.1 mL, 160.3 mmol) and Mg (3.84 g, 160.26 mmol) gives the title

compound (5.32 g, 19.08 mmol, 65%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.36 (s, 9H), 1.50-1.72 (m, 4H), 3.50-3.70 (m, 1H), 4.07 (s, 3H), 6.96 (s, 1H). ES-MS (m/z): calcd for $C_{15}H_{25}N_3O_2$ $(M+H)^+$: 280.4; found : 280.2.

C. 4-(1-Ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[1,2-b]pyridazine.

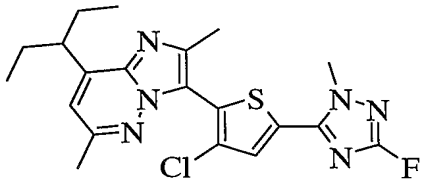
A solution of N-[4-(1-ethyl-propyl)-6-methoxy-pyridazin-3-yl]-2,2-dimethyl-propionamide (5.32 g, 19.08 mmol) in EtOH (250 mL) is treated with $ZnCl_2$ (26.0 g, 190.8 mmol) and refluxed for 48 h. The reaction is cooled to rt and concentrated. The residue is taken up with EtOAc (250 mL), and H_2O (100 mL). It is washed with H_2O (2 x 100 mL); dried with Na_2SO_4; filtered and concentrated. The residue is then dissolved in EtOAc (80 mL), reacted with chloroacetone (1.6 mL, 20.03 mmoL) at reflux overnight. While it is hot, $NaHCO_3$ (8.10 g) is added and the reaction is refluxed for 1 h. It is cooled to rt and filtered through silica gel washed with EtOAc and concentrated. Purification of the crude material by chromatography gives the title compound (0.48 g, 2.07 mmol, 11%). 1H NMR (CDCl3): δ. 0.84 (t, J = 7.5 Hz, 6H), 1.69-1.869 (m, 4H), 2.45 (s, 3H), 3.19-3.30 (m, 1H), 3.94 (s, 3H), 6.39 (s, 1H), 7.49 (s, 1H). ES-MS (m/z): calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.3; found : 234.1.

D. 3-[3-Chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

A solution of 4-(1-ethyl-propyl)-2-methoxy-6-methyl-pyrrolo[*1,2-b*]pyridazine (74.8 mg, 0.32 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-^1H-[1,2,4]triazole (107.5 mg, 0.38 mmol), TDBPP (10.4 mg, 0.016 mmol), tetrabutylammonium bromide (103.0 mg, 0.32 mmol), KOAc (158 mg, 1.61 mmol) in NMP (15 mL) is purged with N2 for 5 min. Pd(OAc)2 (3.6 mg, 0.016 mmol) is added and the resulting mixture is stirred at 125 °C for 6 h. The reaction is cooled to rt, and diluted with EtOAc (10 mL); filtered through silica gel; washed with EtOAc (3 x 30 mL). The filtrate is washed with H2O (3 x 30 m); dried with Na2SO4, filtered and concentrated. Purification of the crude material by silica gel chromatography gives the title compound (0.1062 g, 0.2469 mmol, 77%). 1H NMR (CDCl3): δ. 0.89 (t, J = 7.6 Hz, 6H), 1.75-1.90 (m, 4H), 2.52 (s, 3H), 3.22-3.38 (m, 1H), 3.93 (s, 3H), 4.15 (s, 3H), 6.52 (s, 1H), 7.48 (s, 1H), 7.91 (s, 1H). ES-MS (m/z): calcd for $C_{20}H_{23}ClN_6OS$ $(M+H)^+$: 431.9; found: 431.3.

Example 239.

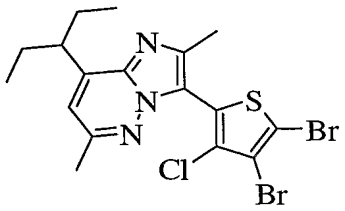
Preparation of 3-[3-chloro-5-(5-fluoro-2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



To a –78 °C solution of 3-[3-chloro-5-(2-methyl-*2H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.40 g, 0.72 mmol) and THF (8 mL) is added 1.7 M *tert*-BuLi (0.47 mL, 0.80 mmol). After 30 minutes the solution is transferred via a cannula into a solution of N-fluorobenzenesulfonamide (0.40 g, 1.25 mmol) and THF. After 30 minutes the solution warmed to ambient temperature. The solution is diluted with EtOAc (40 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The solution is purified by ISCO (20%-30% EtOAc gradient) furnish the title compound (0.068 g, 0.16 mmol, 16%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.71-1.93 (m, 4H), 2.53 (s, 3H), 2.54 (s, 3H), 3.26-3.36 (m, 1H), 4.08 (d J = 2.7 Hz, 3H), 6.75 (s, 1H), 7.97 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{22}ClFN_6S$ $(M+H)^+$: 433.2; found: 433.2.

Example 240.

Preparation of Preparation of 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

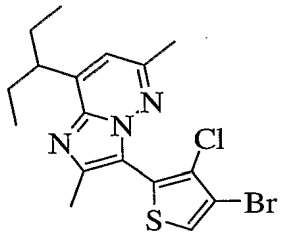


To a solution of 3-(5-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (5.92 g, 14.34 mmol) and triflouroacetic acid (40 mL) and 98% H_2SO_4 (10 ml) is added NBS (3.83 g, 21.15 mmol). After 10 minutes the solution is poured into ice, and made basic with 5M NaOH. The slurry is extracted with

EtOAc (3 x 100 mL), the combined organic layers washed with water (2 x 400 mL), brine (400 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (6.61 g, 13.44 mmol, 94%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.72-1.92 (m, 4H), 2.47 (s, 3H), 2.52 (s, 3H), 3.25-3.34 (m, 1H), 6.72 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{18}Br_2ClN_3S$ $(M+H)^+$: 489.9; found: 490.0.

Example 241.

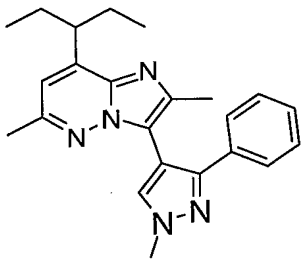
Preparation of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using a procedure similar to Example 76, 3-(4,5-dibromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.83 g, 3.72 mmol), 1.6 M *n*-BuLi (2.56 mL, 4.09 mmol), and THF (30 mL) furnish the title compound (1.05 g, 2.54 mmol, 68%). ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.73-1.92 (m, 4H), 2.48 (s, 3H), 2.51 (s, 3H), 3.27-3.36 (m, 1H), 6.71 (s, 1H), 7.55 (s, 1H). LC/MS (m/z): calcd. for $C_{17}H_{19}BrClN_3S$ $(M+H)^+$: 412.0; found: 412.1.

Example 242.

Preparation of 3-(1-methyl-3-phenyl-^{1}*H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 1-methyl-3-phenyl-^{1}*H*-pyrazole and 1-methyl-5-phenyl-^{1}*H*-pyrazole.

Sodium hydride (60% dispersion in mineral oil, 0.83 g, 20.8 mmol) is suspended in THF (45 ml) and stirred under a nitrogen atmosphere. 3-Phenyl pyrazole (2.5 g, 17.3 mmol dissolved in THF, 15 ml) is added slowly, stirred for 30 minutes then iodomethane (1.3 ml, 20..8 mmol) added and stirred for 3 hrs. The reaction is added to water and extracted twice with ethyl acetate. The combined organic extracts are ished with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 40% ethyl acetate in hexane) to elute the title compound. Obtained is a mixture of 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (2.6g, 95% yield).

B. 4-Bromo-1-methyl-3-phenyl-*1H*-pyrazole and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole.

The mixture of isomers, 1-methyl-3-phenyl-*1H*-pyrazole and 1-methyl-5-phenyl-*1H*-pyrazole (1.0g, 6.3 mmol) and NBS (1.1g, 6.3 mmol) are combined in acetonitrile (25 ml), stirred and heated to 70 °C for 1 hr. The solution is concentrated and the crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 25% ethyl acetate in hexane) to elute 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (504 mg, 34% yield) and 4-bromo-1-methyl-5-phenyl-*1H*-pyrazole (295 mg, 20% yield), respectively:

^{1}H NMR: (400 mHz, DMSO): δ 8.01 (s, 1H), 7.95 (d, 2H), 7.41 (t, 2H), 7.38 (d, 1H), 3.85 (s, 3H).
^{1}H NMR: (400 mHz, DMSO): δ 7.63 (s, 1H), 7.50 (m, 5H) 3.77 (s, 3H).

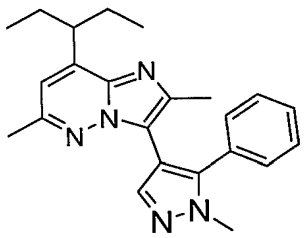
C. 3-(1-Methyl-3-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-3-phenyl-*1H*-pyrazole (250 mg, 1.1 mmol) and cesium carbonate (490 mg, 1.50 mmol) are stirred in DMF (5 ml) and degassed by bubbling a stream of nitrogen through the mixture. $PdCl_2(PPh_3)_2$ (15mg) is added and the mixture is heated to 130^{0}C overnight. The mixture is added to water and extracted twice with ethyl acetate. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude

product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 50% ethyl acetate in hexane) to elute the title compound (17.5 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.68 (s, 1H), 7.37 (m, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 4.04 (s, 3H), 3.36 (m, 1H), 2.38 (s, 3H), 2.15 (s, 3H), 1.82 (m, 4H), 0.86 (t, 6H).

Example 243.

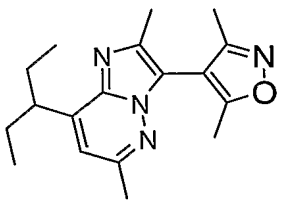
Preparation of 3-(1-methyl-5-phenyl-*1H*-pyrazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (160 mg, 0.73 mmol), 4-bromo-1-methyl-5-phenyl-^1H-pyrazole (250 mg, 1.1 mmol), cesium carbonate (490 mg, 1.50 mmol) and $PdCl_2(PPh_3)_2$ (15 mg) in DMF (5 ml) gives the title compound (18 mg, 4% yield). ES-MS (m/z): calc'd for $C_{23}H_{27}N_5$: 373.5; found 374.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.85 (s, 1H), 7.32 (m, 3H), 7.23 (m, 2H), 6.55 (s, 1H), 3.94 (s, 3H), 3.27 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 (m, 4H), 0.83 (t, 6H).

Example 244.

Preparation of 3-(3,5-dimethyl isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.,

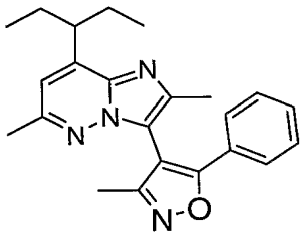


Using the procedure analogous to Example 242, from 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3,5-dimethyl

isoxazole (Alfa, 320 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml), heated at 130 for 4 hrs, then overnight at ambient temperature gives the title compound (65 mg, 23% yield). ES-MS (m/z): calc'd for $C_{18}H_{24}N_4O$: 312.4; found 313.2 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 6.68 (s, 1H), 3.32 (m, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 1.82 (m, 4H), 0.87 (m, 6H).

Example 245.

Preparation of 3-(3-methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.



A. 4-Bromo-3-methyl-5-phenyl isoxazole.

3-Methyl-5-phenyl isoxazole (Synthesis, **1997**, 439-442) (1.0g, 6.3 mmol) and N-bromosuccinimide (1.2 g, 6.9 mmol) are combined together in acetic acid (30 ml) and heated to reflux with stirring for 2 hrs. The solution is added to water and extracted twice with ethyl acetate. The combined organic extracts are washed with sodium bicarbonate (sat'd) and sat. NaCl then dried over Na_2SO_4, filtered and concentrated. The crude product is purified by chromatography using a hexane-ethyl acetate gradient (100% hexane to 10% ethyl acetate in hexane) to elute the title compound (1.5 g, 100% yield). ^1H NMR (400 mHz, $CDCl_3$): δ 8.02 (m, 2H), 7.49 (m, 3H), 6.34, 2.35 (s, 3H).

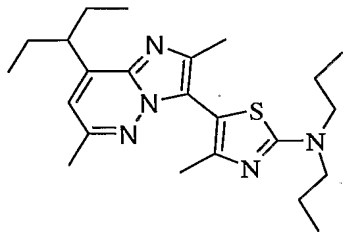
B. 3-(3-Methyl-5-phenyl-isoxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

Using the procedure analogous to Example 257, 8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (200 mg, 0.90 mmol), 4-bromo-3-methyl-5-phenyl isoxazole (430 mg, 1.8 mmol), cesium carbonate (880 mg, 2.70 mmol) and $PdCl_2(PPh_3)_2$ (25mg) in DMF (5 ml) are combined and heated at 130 °C. for 5 hrs to give the title compound (65

mg, 23% yield). ES-MS (m/z): calc'd for $C_{23}H_{26}N_4O$: 374.5; found 375.1 $(M+H)^+$. ^1H NMR (400 mHz, $CDCl_3$): δ 7.50 (d, 2H), 7.31 (m, 3H), 6.69 (s, 1H), 3.39 (m, 1H), 2.48 (s, 3H), 2.20 (s, 6H), 2.33 (s, 3H), 1.84 (m, 4H), 0.88 (m, 6H).

Example 246.

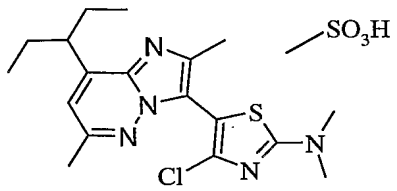
{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-methyl-thiazol-2-yl}-dipropyl-amine.



35 mg of 3-(2-Bromo-4-methyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.09mmol) and 45 mg of di-n-propylamine (0.44 mmol) and 57 mg of cesium carbonate(0.18 mmol) are place into 4 ml reaction vial with 3 ml of dry THF and the vial is capped with a Teflon cap. The reaction vial is heated at 100°C for 4h. The reaction mixture is transferred into microwave reaction vessel and sealed. The reaction mixture is heated at 160°C for 30 min by microwave. The mixture is concentrated and applied onto silica-gel chromatography column (Hexane:AcOEt=3:1) to give the title compound. 5.3 mg (14%); mass spectrum(m/e): 414; ^1H-NMR($CDCl_3$):5.59(s, 1H), 3.45(m, 4H), 3.36(m, 1H), 2.57(s, 3H), 2.47(s, 3H), 2.17(s, 3H), 1.80(m, 8H), 0.99(t, 6H, J=7.5Hz), 0.89(t, 6H, J=9.4Hz).

Example 247.

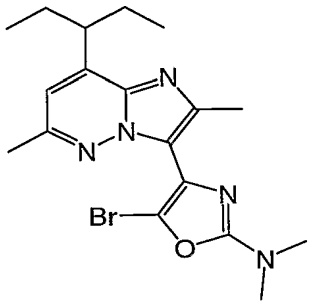
N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine, mesylate salt.



89 mg of N-{5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-chloro-thiazol-2-yl}-dimethylamine (0.236 mmol) is dissolved in 2.0 ml of ethylacetate and 0.236ml of 1M methanesulfonic acid in ethylacetate (0.236 mmol) is added. The solvents are removed under N_2 gas and precipitated crystals are collected, washed with Et2O and dried. 92mg (83%); mass spectrum(m/e): 378(M+1); ^{1}H-NMR($CDCl_3$): 7.30(s, 1H), 3.67(m, 1H), 3.22(s, 6H), 2.93(s, 3H), 2.78(s, 3H), 2.78(s, 3H), 2.71(s, 3H), 1.95(m, 2H), 1.82(m, 2H), 0.96(t, 6H, J=7.3Hz).

Example 248.

Preparation of {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine.

500 mg of 8-(1-ethyl-propyl)-3-iodo-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (1.46 mmol) , 622 mg of oxazole (9.0mmol), 79 mg of triphenylphosphine (0.3 mmol) and 989 mg of cesium carbonate (3.03 mmol) are placed into reaction vial with 7 ml of dry DMF. N_2 gas is bubbled into the mixture for 30 min and 67 mg of Pd_2dba_3 (0.07 mmol) is added. The reaction vial is capped with a Teflon cap and stirred at 130°C for 3 days. The reaction mixture is diluted with dichloromethane, washed with sat NaCl, dried over Na_2SO_4 and evaporated. The crude product is applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give the title compound 172 mg (42%); mass spectrum(m/e): 285; ^{1}H-NMR($CDCl_3$): 8.04(s, 1H), 7.97(s, 1H), 6.78(s, 1H), 3.35(m, 1H), 2.80(s, 3H), 2.65(s, 3H), 1.86(m, 4H), 0.88(t, 6H).

B. 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

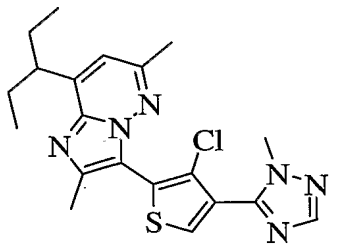
172 mg of 8-(1-ethyl-propyl)-2,6-dimethyl-3-oxazol-4-yl-imidazo[*1,2-b*]pyridazine (0.60 mmol) and 270 mg of NBS (1.51 mmol) are dissolved in 8.0 ml of dichloromethane and stirred at room temperature overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:EtOAc = 3:1) to give 70 mg of the title compound (26%); mass spectrum(m/e): 442; ^{1}H-NMR($CDCl_3$): 6.82(s, 1H), 3.32(m, 1H), 2.59(s, 3H), 2.54(s, 3H), 1.86(m, 4H), 0.89(t, 6H, J=7.4Hz).

C. {5-Bromo-4-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-oxazol-2-yl}-dimethyl-amine.

67 mg of 3-(2,5-Dibromo-oxazol-4-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.15 mmol), 146 mg of cesium carbonate (0.45 mmol) and 3.0 ml of dimethylamine 2.0M in THF (6 mmol) are placed into a 4 ml of reaction vial and the vial is capped with a Teflon cap. The reaction vial is heated at 130°C overnight. The reaction mixture is concentrated and applied onto a silica-gel chromatography column (Hexane:AcOE t = 3:1) to give 53 mg of the title compound (87%); mass spectrum(m/e): 406; ^{1}H-NMR($CDCl_3$): 6.72(s, 1H), 3.37(m, 1H), 3.15(s, 6H), 2.58(s, 3H), 2.53(s, 3H), 1.85(m, 4H), 0.90(t, 6H, J=7.2Hz).

Example 249.

Preparation of 3-[3-chloro-4-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

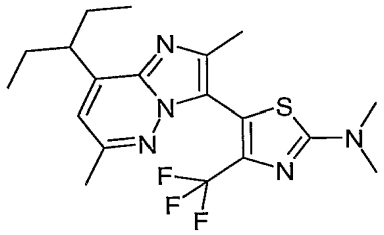


To a flask of 3-(4-bromo-3-chloro-thiophen-2-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.20 g, 0.49 mmol) is added 0.5 g/ mL Reike® Zn (1.3 mL, 0.97 mmol). The slurry is heated at 65 °C for 1 hour, placed in a centrifuge for 5 minutes, and the solution transferred to a flask containing 5-bromo-1-methyl-*1H*-[1,2,4]triazole (0.12 g, 0.73 mmol) and PdCl2(dppf) (0.018 g, 0.024 mmol). The

solution is heated at 65 °C overnight, diluted with EtOAc (20 mL), washed with sat. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO flash chromatography (20%-50% EtOAc gradient) furnish the title compound (0.018 g, 0.043 mmol, 9%). ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 6H), 1.74-1.92 (m, 4H), 2.51 (s, 3H), 2.52 (s, 3H), 3.26-3.37 (m, 1H), 3.95 (s, 3H), 6.72 (s, 1H), 7.82 (s, 1H), 8.01 (s, 1H). LC/MS (m/z): calcd. for $C_{20}H_{23}ClN_6S$ $(M+H)^+$: 415.2; found: 415.3.

Example 250.

Preparation of {5-[8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.



A. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine.

Iodoimidazopiridazine (6.75 g, 19.7 mmol), triphenylphosphine (1.03 g, 3.94 mmol), Cs_2CO_3 (12.84 g, 39.4 mmol) and $Pd_2(dba)_3$ (900 mg, 0.98 mmol) are put into a sealed tube with 65 mL of dry DMF and N_2 gas is bubbled into the mixture for 5 minutes. Thiazole (8.36 g, 6.7 mL, 98.4 mmol) is added, and the mixture is heated at 130°C overnight. The mixture is cooled to r.t. and quenched by addition of NH_4Cl saturated solution (200 mL). The mixture is extracted with Et_2O (3 x 100 mL) and the organic layers washed with water (2 x 100 mL) and sat. NaCl (100 mL), dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent; hexane:EtOAc= 4:1) to give 3.80 g of the title compound (Yield: 64%). ESIMS: m/z 301 $[M+H]^+$.

B. 3-(2,4-Dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-thiazol-5-yl-imidazo[*1,2-b*]pyridazine. (3.80 g, 12.6 mmol) in CH_3CN (55 mL) at room temperature is added NBS (5.18 g, 29.1 mmol), and the mixture is stirred at room temperature for 3 hours. A white precipitate is formed that is filtered in vacuo, to give 4.86 g of the title compound (Yield: 84%). ESIMS: m/z 459, 461 $[M+H]^+$.

C. 3-(4-Bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(2,4-dibromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (4.86 g, 10.6 mmol) in THF (150 mL) under N_2 atmosphere at –78°C, BuLi (6.63 mL 1.6 M in hexane, 10.6 mmol) is added dropwise for a period of 10 minutes. The mixture is stirred at –78°C for 30 minutes. Water is added, and the mixture is extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to give 3.28 g of the title compound (Yield: 82%). ESIMS: m/z 379, 381 $[M+H]^+$.

D. 8-(1-Ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine.

To a solution of 3-(4-bromo-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (2.45 g, 6.5 mmol) in NMP (35 mL) in a sealed tube is added $FSO_2CF_2CO_2Me$ (2.5 g, 1.65 mL, 13 mmol) and CuI (2.48 g, 13 mmol). N_2 gas is bubbled into the mixture for 5 minutes, and the mixture is heated at 120°C for 9 hours. After cooling to room temperature, water (100 mL) and NaCl saturated solution (100 mL) are added to the mixture. The mixture is extracted with Et_2O (5 x 80 mL); washed with water (2 x 100 mL), and dried over $MgSO_4$ and concentrated. The crude product is purified by flash chromatography on silica gel (eluent hexane:EtOAc 5:1) to obtain 960 mg of the title compound (Yield: 40%). ESIMS: m/z 369 $[M+H]^+$.

E. 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine.

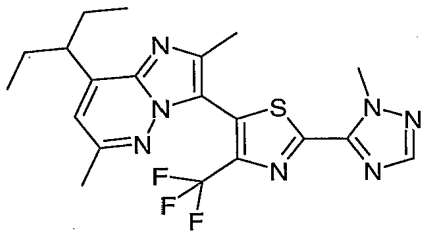
To a solution of 8-(1-ethyl-propyl)-2,6-dimethyl-3-(4-trifluoromethyl-thiazol-5-yl)-imidazo[*1,2-b*]pyridazine (915 mg, 2.48 mmol) in 40 mL of THF under N_2 atmosphere al –78°C, BuLi (1.86 mL 1.6 M in hexane, 2.98 mmol) is slowly added. The mixture is stirred at –78°C for 30 minutes. Then, a solution of CBr_4 (989 mg, 2.98 mmol) in 3 mL of THF is added, and the mixture is stirred at –78°C for 45 minutes. The reaction is quenched by addition of NH_4Cl saturated solution (50 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product is purified by flash chromatography on silica gel (eluent CH_2Cl_2) to obtain 685 mg of the title compound (Yield: 62%). ^{1}H NMR ($CDCl_3$): δ0.86 (t, J = 7.5 Hz, 6H), 1.82 (m, 4H), 2.45 (s, 3H), 2.51 (s, 3H), 3.27 (m, 1H), 6.74 (s, 1H). ESIMS: m/z 447, 449 $[M+H]^+$.

F. {5-[8-(1-Ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine.

100 mg of 3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine (0.22 mmol) and 218 mg of cesium carbonate (0.66 mmol) are placed in 4 ml reaction vial and 3 ml of dimethylamine 2 M in THF is added. The reaction vial is capped with a Teflon cap and heated at 120°C overnight. The reaction mixture is filtered and concentrated and applied onto a silica-gel chromatography column (Hexane :AcOEt =3:1) to give 85 mg of the title compound. Yield 94%. mass spectrum (m/e) : 412 (M+1).

Example 251.

Preparation of 8-(1-Ethyl-propyl)-2,6-dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-4-trifluoromethyl-thiazol-5-yl]-imidazo[*1,2-b*]pyridazine

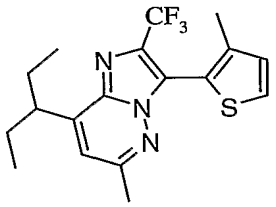


164 mg of 1-Methyl-1,2,4-triazole (1.96 mmol) is dissolved in 2 ml of THF and cooled to –78 °C. 0.8 ml of 2.5M n-butyllithium in hexane (1.96 mmol) is added slowly and stirred at –78 °C, warmed up to room temperature and stirred at r.t. for 15min and

cooled to –78 °C. 3.96 ml of 0.5 M $ZnCl_2$ in THF (1.98 mmol) is added and stirred at room temperature for 15 min. 180 mg of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-8-(1-ethyl-propyl)-2,6-dimethyl-imidazo[*1,2-b*]pyridazine and 54 mg of PdCl2(pddf) (0.06 mmol) are added. The vial is capped with a Teflon cap and heated at 80 °C overnight. NH_4Cl aq. is added to quench the reaction and the mixture is extracted by CH_2Cl_2, dried over Na2SO4 and evaporated. The crude product is applied onto silica-gel chromatography column (Hexane :AcOEt=3:1) to give 119 mg of the title compound. Yield 58%. mass spectrum (m/e) : 449(M+1).

Example 252.

Preparation of 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



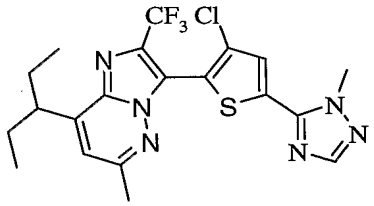
A. 8-(1-Ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

α-Bromotrifluoroacetone (402 mg, 2.93 mmol) is added to a dry 10 mL microwave reaction tube containing 4-(1-ethyl-propyl)-6-methyl-pyridazin-3-ylamine (500 mg, 2.79 mmol) in EtOH (2.0 mL). The resulting mixture is heated at 110 °C in the microwave for 1 hour. $NaHCO_3$ (246.5 mg, 2.93 mmol) is added, and the reaction is mixed well for 5 minutes. Then, the reaction is heated at 110 °C in the microwave for 1 hour. The solvent is removed via reduced pressure, and the reaction is diluted with ethyl acetate (30 mL). The organic layer is washed with H_2O (3 X 10 mL), and the combined aqueous layers are extracted with ethyl acetate (2 X 20 mL). The combined organic extracts are dried over Na_2SO_4, filtered, and purified by silica gel chromatography to give the title compound (29.5 mg, 0.068 mmol, 9.8 %). ^{1}H-NMR ($CDCl_3$), δ 0.87 (t, J = 7.6 Hz, 6H), 1.86 (m, 4H), 2.60 (s, 3H), 3.30 (m, 1H), 6.80 (s, 1H), 8.14 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{13}H_{16}F_3N_3$ $(M+H)^+$: 271.29; found: 272.2

B. 8-(1-Ethyl-propyl)-6-methyl-3-(3-methyl-thiophen-2-yl)-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

To a dry 10 ml round bottom flask with reflux condenser containing 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (300 mg, 1.11 mmol), 2-bromo-3-methyl-thiophene (216 mg, 1.22 mmol), and Cs_2CO_3 (760 mg, 2.33 mmol) is added NMP (1.7 ml). The mixture is degassed with bubbling N_2 for 15 min and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol) and PPh_3 (58.2 mg, 0.222 mmol) are added. The reaction mixture is stirred at 130°C overnight. The mixture is cooled to rt, diluted with H_2O; and extracted with EtOAc (3 x 20 ml). The organic layers are dried (Na_2SO_4), filtered and purified by HPLC to give title compound (32 mg, 0.087 mmol, 8%). ^{1}H-NMR ($CDCl_3$), δ 0.93 (t, J = 7.2 Hz, 6H), 1.91 (m, 4H), 2.15 (s, 3H), 2.58 (s, 3H), 3.36 (m, 1H), 6.91 (s, 1H), 7.08 (d, J = 5.3 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{20}F_3N_3S$ $(M+H)^+$: 367.44; found: 368.1.

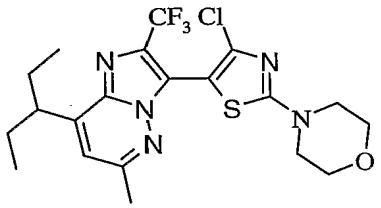
Example 253.Preparation of 3-[3-Chloro-5-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiophen-2-yl]-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (182 mg, 0.671 mmol), 5-(5-bromo-4-chloro-thiophen-2-yl)-1-methyl-*1H*-[1,2,4]triazole (225 mg, 0.805 mmol), KOAc (330.2 mg, 3.36 mmol), and TBAB (217 mg, 0.671 mmol) are dissolved in NMP (3 mL). The mixture is degassed with bubbling nitrogen for 20 minutes. Then, $Pd(OAc)_2$ (8 mg, 0.034 mmol) and TDBPP (20.4 g, 0.34 moles) are added. The reaction mixture is heated to 125 °C for 3 hours to give the title compound (125 mg, 0.267 mmol, 40%). ^{1}H-NMR ($CDCl_3$), δ 0.88 (t, J = 7.2 Hz, 6H), 1.87 (m, 4H), 2.537 (s, 3H), 3.32 (m, 1H), 4.16 (s, 3H), 6.86 (s, 1H), 7.51 (s, 1H), 7.91 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{20}H_{20}ClF_3N_6S$ $(M+H)^+$: 468.93; found: 469.2.

Example 254.

Preparation of 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.



A. 8-(1-Ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (460 mg, 1.70 mmol) are dissolved in dry THF (3.5 mL) and cooled to -78°C. A solution of 2.5 M *n*-butyllithium in hexanes (748 µL, 1.87 mmol) is added dropwise. The reaction mixture is stirred for 20 minutes at -78 °C, then warmed to 0 °C for 15 minutes. A solution of I_2 (453 mg, 1.79 moles) in THF (2.0 mL) is added dropwise. The reaction is stirred for 15 minutes at 0 °C, and then warmed to room temp. The reaction is stirred overnight, and the solvent is removed via reduced pressure. The reaction mixture is redissolved in ethyl acetate (50 mL) and washed with a 1 N solution of $Na_2S_2O_3$ (2 X 20 mL). The aqueous layer is extracted with ethyl acetate (2 X 40 mL). The combined organic extracts are dried with Na_2SO_4, filtered, and purified via silica gel chromatography to give the title compound (595 mg, 1.50 mmol, 88%). ^{1}H-NMR ($CDCl_3$), δ 0.82 (t, J = 8.0 Hz, 6H), 1.83 (m, 4H), 2.64 (s, 3H), 3.27 (m, 1H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{13}H_{15}F_3IN_3$ $(M+H)^+$: 397.18; found: 398.3.

B. 2,4-Dichloro-thiazole.

In a 250 mL round bottom flask, 2.4-thiazolidine dione (12.5 g, 107 mmol) is dissolved in phosphorousoxychloride (70 mL) and pyridine (8.5 mL). The mixture is stirred under reflux for 3 hours and cooled to room temp. The reaction mixture is poured into ice water slowly and extracted with dichloromethane. The combined organic extracts are dried with Na_2SO_4, filtered, and concentrated. The residue is purified via silica gel

chromatography to give title compound (9.18 g, 59.6 mmol, 56%). ^{1}H-NMR ($CDCl_3$), δ 7.01 (s, 1H) ppm.

C. 4-(4-Chloro-thiazol-2-yl)-morpholine.

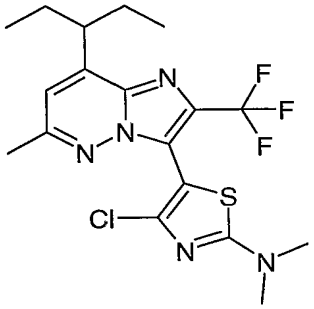
In a 75 mL dry pressure vessel, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and morpholine (560 μL, 6.4 mmol) are dissolved in dry THF (2.0 mL). Cs_2CO_3 (1.56 g, 4.8 mmol) is added, and the reaction vessel is sealed. The reaction mixture is heated to 110 °C overnight. Solvent is removed via reduced pressure, and the crude reaction mixture is purified via silica gel chromatography to give the title compound (597 mg, 2.92 mmol, 91%). ^{1}H-NMR ($CDCl_3$), δ 3.45 (m, 4H), 3.79 (m, 4H), 6.31 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_7H_9ClN_2OS$ $(M+H)^+$: 204.68; found: 205.2.

D. 3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine.

In a dry 25 mL round bottom flask, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol), 4-(4-chloro-thiazol-2-yl)-morpholine (194 mg, 0.945 mmol), and Cs_2CO_3 (410 mg, 1.26 mmol) are dissolved in DMF. The mixture is degassed with bubbling nitrogen for 15 minutes. Then, $Pd_2(dba)_3$ (18 mg, 0.032 mmol) and PPh_3 (33 mg, 0.126 mmol) are added. The reaction mixture is heated to 130 °C overnight. The reaction is cooled to room temp., quenched with a solution of NH_4Cl sat? (20 mL), and extracted with Et_2O (3 X 50 mL). The combined organic extracts are washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated. The residue is purified via reverse phase HPLC with a 30-80% gradient of CH_3CN in 10mM NH_4HCO_3/H_2O/5%CH_3CN (pH 10.0)to give the title compound (11 mg, 0.023 mmol, 4%). ^{1}H-NMR ($CDCl_3$), δ 0.86 (t, J = 7.3 Hz, 6H), 1.84 (m, 4H), 2.55 (s, 3H), 3.31 (m, 1H), 3.54 (dd, J = 5.2, 4H), 3.84 (dd, J = 5.2 Hz, 4H), 6.82 (s, 1H) ppm. ES$^-$MS (m/z): calcd for $C_{20}H_{23}ClF_3N_5OS$ $(M+H)^+$: 473.95; found: 474.2.

Example 255.

Preparation of {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.



A. (4-Chloro-thiazol-2-yl)-dimethyl-amine.

Using a procedure analogous to Example 254C, 2,4-dichloro-thiazole (500 mg, 3.2 mmol) and dimethylamine (a 2.0 M solution in THF, 3 mL, 6.4 mmol) are reacted to give the title compound (60 mg, 0.152 mmol, 15%). ^{1}H-NMR ($CDCl_3$), δ 3.09 (s, 6H), 6.22 (s, 1H) ppm. ES-MS (m/z): calcd for $C_5H_7ClN_2S$ $(M+H)^+$: 162.64; found: 163.2.

B. {4-Chloro-5-[8-(1-ethyl-propyl)-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazin-3-yl]-thiazol-2-yl}-dimethyl-amine.

Using a procedure analogous to Example 254D, 8-(1-ethyl-propyl)-3-iodo-6-methyl-2-trifluoromethyl-imidazo[*1,2-b*]pyridazine (250 mg, 0.630 mmol) is coupled with (4-chloro-thiazol-2-yl)-dimethyl-amine (154 mg, 0.945 mmol) to provide desired product. ^{1}H-NMR ($CDCl_3$), δ 0.85 (t, J = 7.4 Hz, 6H), 1.83 (m, 4H), 2.55 (s, 3H), 3.16 (s, 6H), 3.31 (m, 1H), 6.81 (s, 1H) ppm. ES-MS (m/z): calcd for $C_{18}H_{21}ClF_3N_5S$ $(M+H)^+$: 431.91; found: 432.2.

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert *et al.*, *EJP* 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ^{125}I-

sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 199 provides an ED_{50} result of 1.3 mg/kg.

Example B

CRF1 Filter Binding Assay

The limitations of plasmid-based human CRF1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 µl of ^{125}I-sauvagine (0.2 nM final), 50 µl compound and 100 µl CRF1 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are wash twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

Using this assay, the claimed exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 µM. For example, Examples 102 and 199 exhibit a Ki of 4.92 ± 0.57 nM and 9.98 ± 0.72 nM, respectively.

Example C

CRF2 Filter Binding Assay

The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 µl) are set up as follows: 50 ul of ^{125}I-sauvagine (0.2 nM final concentration), 50 µl compound and 100 µl CRF2 membrane (25 µg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold

assay buffer (50 mM tris, 12.5 mM NaCl, 1mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 µl Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 µM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50ul of ^{125}I-Sauvagine (0.2 nM final concentration), 50 µl compound or non-labelled sauvagine (NSB) and 100 µl containing 250 µg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 µg/reaction). Plates are incubated for 4-5 hours at room temperature and then centrifuged at 200 X g for 10 minutes. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

Compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Examples 102 and 199 exhibit a percent inhibition at 50 µM of 9.0 ± 2.6 and 16.9 ± 1.9, respectively. These results suggest that the compounds of the present invention are highly selective for the CRF1 receptor.

Example D

Bioavailability and Pharmacokinetic Properties

The compounds of Formula I are antagonists of CRF1, and possess surprisingly useful properties related to their pharmacokinetics and bioavailability.

The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical

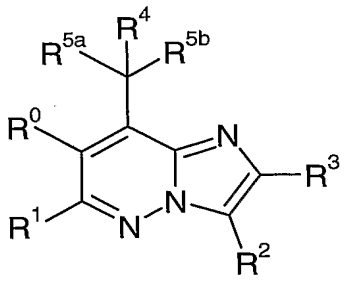
setting, Vdist can be used to determine a loading dose achieve a steady state concentration.

To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 3 mg/kg intravenous dose of compound. Multiple plasma samples are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (Clp).

An overwhelming majority of commercial CNS and cardiovascular drugs exhibit a human Vdist of <10 L/Kg. In comparison with CRF antagonists CP154526 (Schulz et al., *Proc. Natl. Acad. Sci. (USA)*, 93:10477 (1996)) and NBI30775 (Chen et al., *Drug Development Research*, 65:216 (2005)) which exhibit a rat Vdist of 114 L/Kg and 76 L/Kg, respectively, following a single intravenous dose, thiazole Examples 48 and 199 of the present invention exhibits a rat Vdist of only 9 and 2 L/Kg, respectively. Furthermore, thiophene Examples 88 and 39 of the present invention exhibit a rat Vdist of only 44 and 17 L/kg, respectively.

WE CLAIM:

1. A compound of Formula I



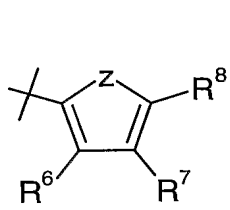
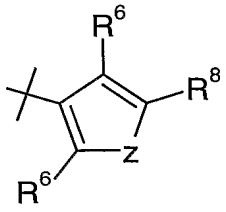
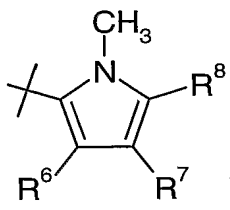
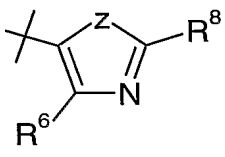
Formula I

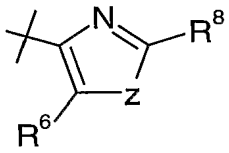
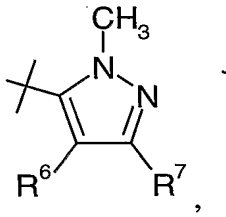
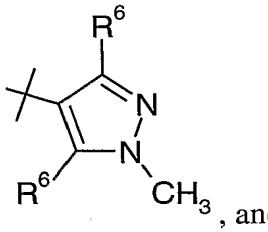
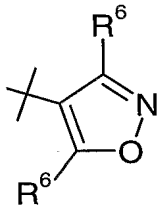
wherein:

R^0 is hydrogen, halo, methyl or ethyl;

R^1 and R^3 are independently methyl, methoxy, or trifluoromethyl;

R^2 is selected from the group consisting of:

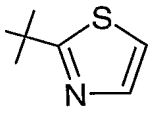
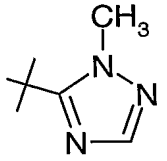
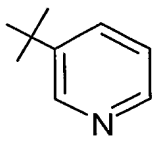
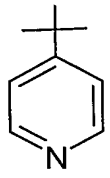
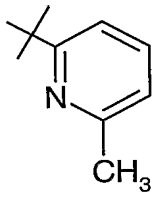
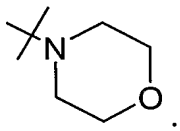
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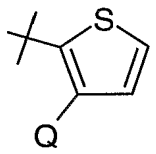
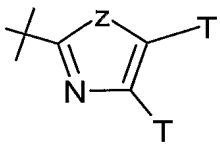
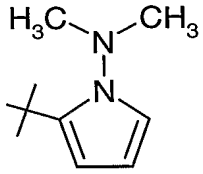
R^4 is hydrogen, halo, or hydroxy;

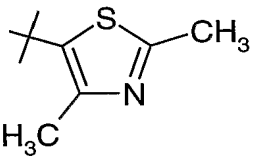
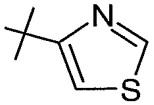
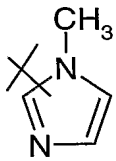
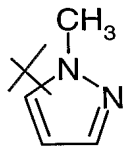
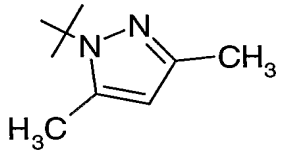
R^{5a} and R^{5b} are independently ethyl or n-propyl;

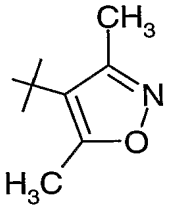
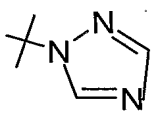
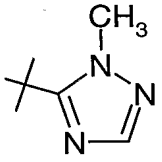
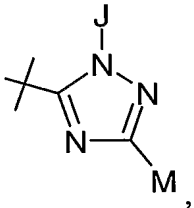
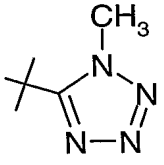
R^6 at each occurrence is independently hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, trifluoromethyl, methoxy, or phenyl;

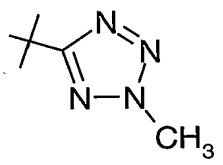
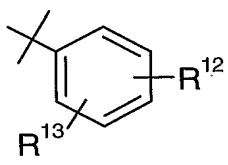
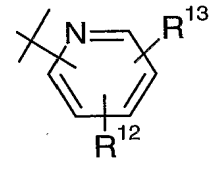
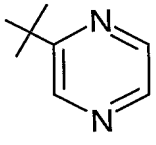
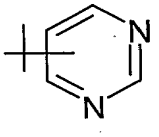
R^7 is hydrogen, halo, methyl, methoxy, dimethylamino,  ,  ,  ,  ,  , or  ;

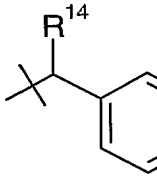
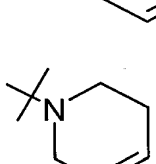
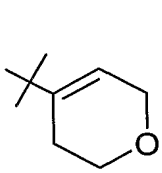
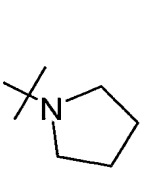
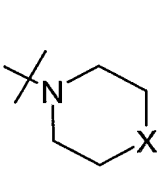
R^8 is selected from the group consisting of hydrogen, halo, cyano, $(C_1\text{-}C_4)$alkyl, R^aR^bN-, carbamyl, $(C_1\text{-}C_2)$alkoxy$(C_1\text{-}C_2)$alkyl, R^{11}-C(O)-,

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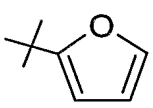
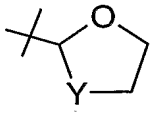
 ,  ,  ,  ,  , or ;

R^{11} is methoxy, methylamino, dimethylamino, or phenyl;

R^{12} is hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy dimethylamino, acetyl, or methylsulfonyl;

R^{13} is hydrogen, methyl or halo;

R^{14} is hydrogen or hydroxy;

R^{15} is methylthio, cyclopropyl, phenyl,  or  ;

R^a is hydrogen, $(C_1\text{-}C_5)$alkyl, $(C_3\text{-}C_5)$cycloalkyl, methoxy$(C_2\text{-}C_4)$alkyl, acetyl, $(C_1\text{-}C_2)$alkylsulfonyl, (C_3)alkenyl, $R^{15}\text{-}(CH_2)n\text{-}$, or $(C_1\text{-}C_2)$alkyl substituted with cyano, formyl, vinyl, or ethynyl;

R^b is hydrogen or $(C_1\text{-}C_3)$alkyl;

X is $-CH_2-$, -CO-, -O-, -S- or $-SO_2-$;

Y is $-CH_2-$ or -O-;

z is S or O;

n is 1 or 2;

Q is hydrogen or methyl;

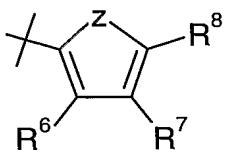
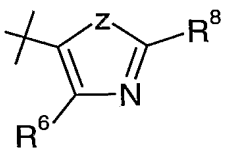
T is hydrogen or methyl;

J is methyl, trifluoroethyl, or tert-butyl; and

M is methyl or halo;

and pharmaceutically acceptable salts thereof.

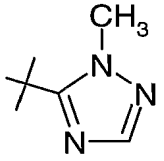
2. The compound of Claim 1 wherein R^0 and R^4 are hydrogen, R^1 and R^3 are methyl, and R^{5a} and R^{5b} are ethyl.

3. The compound according to any one of claims 1 to 2, wherein R^2 is selected from the group consisting of  or  and where z is S.

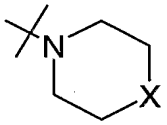
4. The compound according to any one of claims 1 to 3, wherein R^7 is hydrogen.

5. The compound according to any one of claims 1 to 4, wherein R^6 is halo or methyl.

6. The compound according to any one of claims 1 to 5, wherein R^8 is



or



and where X is O.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

8. A compound according to any one of Claims 1 to 6 for use as a medicament.

9. Use of a compound according to any one of Claims 1 to 6 for the manufacture of a medicament for treating anxiety, depression, major depressive disorder, alcohol withdrawal symptoms, or irritable bowel syndrome in a mammal.

10. Use of a compound according to Claim 9 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 1 364 952 A (EISAI CO., LTD) 26 November 2003 (2003-11-26) examples	1-10
A	WO 97/29109 A (JANSSEN PHARMACEUTICA N.V; NEUROCRINE BIOSCIENCES INC; CHEN, CHEN; WEB) 14 August 1997 (1997-08-14) examples	1-10
A	EP 1 466 527 A (SUMITOMO CHEMICAL TAKEDA AGRO COMPANY, LIMITED) 13 October 2004 (2004-10-13) examples	1-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2006	16/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Menegaki, F

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009942

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOREAU S ET AL: "Synthesis and anticonvulsant Properties of Triazolo- and Imidazopyridazinyl Carboxamides and Carboxylic Acids" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 6, no. 7, July 1998 (1998-07), pages 983-991, XP002991062 ISSN: 0968-0896 compounds 9,10,11 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/009942

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		WO	03061388 A1	31-07-2003
		US	2005032650 A1	10-02-2005

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 094 709 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
15.09.2010 Bulletin 2010/37

(21) Application number: **07842582.4**

(22) Date of filing: **17.09.2007**

(51) Int Cl.:
C07D 487/04 *(2006.01)* ***A61K 31/505*** *(2006.01)*
A61P 29/00 *(2006.01)* ***A61P 25/22*** *(2006.01)*
A61P 25/24 *(2006.01)* ***A61P 25/30*** *(2006.01)*

(86) International application number:
PCT/US2007/078605

(87) International publication number:
WO 2008/036579 (27.03.2008 Gazette 2008/13)

(54) **THIAZOLE PYRAZOLOPYRIMIDINES AS CRF1 RECEPTOR ANTAGONISTS**

THIAZOLPYRAZOLOPYRIMIDINE ALS ANTAGONISTEN DES CRF1-REZEPTORS

THIAZOLE PYRAZOLOPYRIMIDINES CONVENANT COMME ANTAGONISTES DU RÉCEPTEUR DU CRF1

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK RS

(30) Priority: **20.09.2006 US 826264 P**

(43) Date of publication of application:
02.09.2009 Bulletin 2009/36

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WO-A-00/59908 **WO-A-01/23388**
WO-A-97/29109 **WO-A-98/03510**
WO-A-02/072202 **WO-A-2005/063755**

- **GEHLERT ET AL: "3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1 ,2-b]pyridazine: a novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism." THE JOURNAL OF NEUROSCIENCE, vol. 27, no. 10, 7 March 2007 (2007-03-07), pages 2718-2726, XP002465426**
- **HE LIQI ET AL: "4-(1,3-Dimethoxyprop-2-ylamino)-2,7-dimet hyl-8-(2,4- dichlorophenyl) pyrazolo[1,5-a]-1,3,5-triaz ine: A Potent, Orally Bioavailable CRF1 Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 449-456, XP002196777 ISSN: 0022-2623**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

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(Cont. next page)

- CHEN C ET AL: "DESIGN OF 2,5-DIMETHYL-3-(6-DIMETHYL-4-METHYLPYRIDIN -3-YL)-7-DIPROPYL AMINOPYRAZOLO[1,5-ALPHA] PYRIMIDINE (NBI 30775/R121919) AND STRUCTURE-ACTIVITY RELATIONSHIPS OF A SERIES OF POTENT AND ORALLY ACTIVE CORTICOTROPIN-RELEASING FACTOR RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 19, 9 September 2004 (2004-09-09), pages 4787-4798, XP001206057 ISSN: 0022-2623

Description

FIELD OF THE INVENTION

[0001] This invention relates to novel thiazole pyrazolopyrimidine compounds, pharmaceutical compositions thereof, and use thereof as CRF' I receptor antagonists in the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome.

BACKGROUND OF THE INVENTION

[0002] Corticotropin releasing factor (CRF) is a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors.

[0003] CRF has been implicated in psychiatric disorders and neurological diseases including depression and anxiety, as well as the following: Alzheimer's disease, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy, migraine, alcohol and substance abuse and associated withdrawal symptoms, obesity, metabolic syndrome, congenital adrenal hyperplasia, Cushing's disease, hypertension, stroke, irritable bowel syndrome, stress-induced gastric ulceration, premenstrual syndrome, sexual dysfunction, premature labor, inflammatory disorders, allergies, multiple sclerosis, visceral pain, sleep disorders, pituitary tumors or ectopic pituitary-derived tumors, chronic fatigue syndrome and fibromyalgia.

[0004] CRF receptor subtypes, CRF1 and CRF2, have been identified and are distributed heterogeneously within the brain thereby suggesting potential functional diversity. For example, widely distributed brain CRF I receptors are strongly implicated in emotionality accompanying exposure to environmental stressors. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors. A more discrete septal/hypothalmic distribution and the availability of alternative endogenous ligands suggest a different functional role for the CRF2 receptor. For example, a novel CRF-family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism. In other cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF1 gene deletion. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF1 antagonists may be an important treatment for obesity as well.

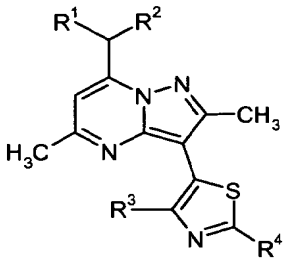
[0005] Certain pyrrolo[2,3-*d*]pyrimidines, pyrrolo[3,2-*d*]pyrimidines, pyrazolo[1,5-*a*]pyrimidines, 1,2,3-triazolo[4,5-*b*] pyridines, and pyrazolo[1,5-*a*]-1,3,5-triazines, useful as CRF antagonists, are described in WO 94/13676, WO 97/29109, WO 98/08847, and WO 98/03510. WO 00/59908 discloses certain pyrazolo[1,5-*a*] pyrimidines which are described as CRF antagonists. WO 2005/063755 discloses a genus of compounds encompassing pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidin-2-ones, the compounds in this genus are also described as CRF antagonists. The CRF antagonists 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine and 4-(2-butylamino)-2,7-dimethyl-8-(2-methyl-6-methoxypyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazine are disclosed in J. Neuroscience, Vol. 27, No. 10, 2718-2726 (2007) and WO 02/072202, respectively. He et al. describe in J. Med. Chem., Vol. 43, 449-456 (2000) SAR studies in the pyrazolo[1,5-a]-1,3,5-triazine series leading to the discovery of the CRF antagonist 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)-pyrazolo[1,5-*a*]-1,3,5-triazine. Chen et al. in J. Med. Chem., Vol. 47, 4787-4798 (2004) describe a series of 3-pyridylpyrazolo[1,5-*a*]pyrimidines, which are described a CRF antagonists.

[0006] WO 01/23388 discloses certain amino-substituted pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]-1,3,5-triazines which are described as selective modulators of mammalian neuropeptide Y_1 (NPYI) receptor.

[0007] The present invention provides novel thiazole pyrazolopyrimidines useful as CRF1 receptor antagonists. In view of the above, it is desirable to discover new efficacious and selective antagonists of CRF 1 as potentially valuable therapeutic agents for the treatment of psychiatric and neuroendocrine disorders, neurological diseases, and metabolic syndrome. Further, since a majority of commercial CNS and cardiovascular drugs exhibit unfavorable bioavailability and pharmacokinetic profiles, it is also desirable to discover new compounds with favorable bioavailability and pharmacokinetic profiles relative to known CRF antagonists such as CP154526 and NBI30775.

SUMMARY OF THE INVENTION

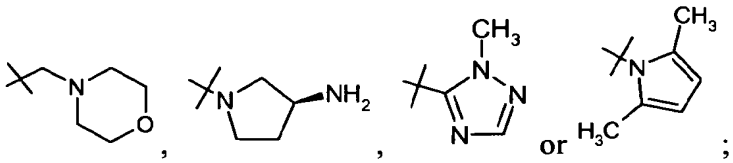
[0008] In one embodiment, the present invention provides a compound of Formula I



Formula I

wherein:

R^1 and R^2 are independently ethyl or *n*-propyl;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, n-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,



R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-; or a pharmaceutically acceptable salt thereof.

[0009] In another embodiment, the present invention provides a pharmaceutical composition comprising: a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0010] In another embodiment, the present invention relates to use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

[0011] In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety, alcohol or substance abuse, obesity, hypertension, metabolic syndrome, irritable bowel syndrome, epilepsy, stroke, sleep disorders, allergy, migraine, premenstrual syndrome, infertility, sexual dysfunction, congenital adrenal hyperplasia, Cushing's disease, premature labor, stress-induced gastric ulceration, inflammatory disorders, pituitary or ectopic pituitary-derived tumors, chronic fatigue syndrome, fibromyalgia, visceral pain or multiple sclerosis.

[0012] In another embodiment, the present invention relates to a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl" means a saturated aliphatic hydrocarbon group, which may be straight or branched, having 1 to 5 carbon atoms in the chain.

"Pharmaceutically acceptable excipient" refers to a pharmaceutically acceptable formulation carrier, solution, or additive to enhance the formulation characteristics. Such excipients must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof and are well known to the skilled artisan (see e.g.

Remingtons Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, 1995).

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed (see *e.g.* Remingtons Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, 1995).

"Therapeutically effective amount" or "effective amount" means the amount of the compound of formula I of the present invention or pharmaceutical composition containing a compound of formula I of the present invention that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0014] The terms "treatment," "treat," "treating," and the like, are meant to include both slowing and reversing the progression of a disorder. These terms also include alleviating, ameliorating, attenuating, eliminating, or reducing one or more symptoms of a disorder or condition, even if the disorder or condition is not actually eliminated and even if progression of the disorder or condition is not itself slowed or reversed. The term "treatment" and like terms also include preventive (e.g., prophylactic) and palliative treatment. Prevention of the disease is manifested by a prolonging or delaying of the onset of the symptoms of the disease.

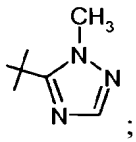
[0015] The symbol "-" in a molecular structure indicates the position of attachment for that particular substituent.

[0016] When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well- known principles of chemical structure connectivity.

[0017] Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, an arylcarbonylaminoalkyl substituent is equivalent to aryl-C(O)-NH-alkyl-.

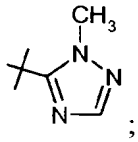
[0018] The present invention contemplates the following embodiments, which can alternatively be further combined:

(a) A compound of Formula I wherein R^1 and R^2 are ethyl;
(b) A compound of Formula I wherein R^1 and R^2 are *n*-propyl;
(c) A compound of Formula I wherein R^3 is Cl, Br, methyl or trifluoromethyl;
(d) A compound of Formula I wherein R^3 is Cl;
(e) A compound of Formula I wherein R^3 is Br;
(f) A compound of Formula I wherein R^4 is R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or



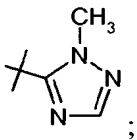
;

(g) A compound of Formula I wherein R^4 is morpholin-4-yl;
(h) A compound of Formula I wherein R^4 is



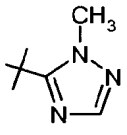
;

(i) A compound of Formula I wherein R^3 and R^b are independently C_1-C_3alkyl;
(j) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Cl, and R^4 is morpholin-4-yl;
(k) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Cl, and R^4 is morpholin-4-yl;
(l) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Br, and R^4 is morpholin-4-yl;
(m)A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Br, and R^4 is morpholin-4-yl;
(n) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Cl, and R^4 is



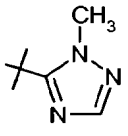
;

(o) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Cl, and R^4 is



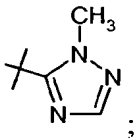
;

(p) A compound of Formula I wherein R^1 and R^2 are ethyl, R^3 is Br, and R^4 is



;

(q) A compound of Formula I wherein R^1 and R^2 are *n*-propyl, R^3 is Br, and R^4 is



;

(r) Use of a compound of Formula I , or a pharmaceutically acceptable salt thereof, for treating depression or anxiety;
(s) Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse;
(t) Use of a comound of Formula I, or a pharmaceutically acceptable salt thereof, for treating alcohol or substance abuse and associated withdrawal symptoms;
(u) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 500 nM;
(v) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 50 nM;
(w)A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 5 nM;
(x) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 500 nM and selectively binding to CRF1 (i.e., lower Ki) relative to CRF2;
(y) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF 1 binding of ≤ 50 nM and selectively binding to CRF 1 (i.e., lower Ki) relative to CRF2;
(z) A compound of Formula I, or a pharmaceutically acceptable salt thereof, exhibiting a Ki value for CRF I binding of ≤ 5 nM and selectively binding to CRF 1 (i.e., lower Ki) relative to CRF2; and/or
(aa) Particular exemplified compounds with superior bioavailability and pharmacokinetic profiles relative to some known CRF antagonists (e.g., CP 154526 and NBI30775), such as Example 15.

[0019] The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by a variety of routes. Preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing same are well known in the art (see, e.g., Remington: The Science and Practice of Pharmacy, A. Gennaro, et al., eds., 19th ed., Mack Publishing Co., 1995).

[0020] The compounds of Formula I are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.0001 to about 30 mg/kg of body weight. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

[0021] The compounds of Formula I are CRF-1 antagonists and, as such, are useful for treating a condition which is treatable by reducing CRF1 receptor tone or stimulation. Corticotropin releasing factor (CRF), a 41 amino acid peptide that is the primary physiological regulator of proopiomelanocortin (POMC) derived peptide secretion from the anterior pituitary gland [J. Rivier et al., Proc. Natl. Acad. Sci (USA) 80:4851 (1983); W. Vale et al., Science 213:1394 (1981)], has been linked to a number of medical conditions. For example, in addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in the brain [W. Vale et al., Rec. Prog. Horm. Res. 39:245 (1983); G. F. Koob, Persp. Behav. Med. 2:39 (1985); E. B. De Souza et al., J. Neurosci. 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response in the immune system to physiological, psychological, and immunological stressors [see, e.g., J. E. Blalock, Physiological Reviews 69:1 (1989); J. E. Morley, Life Sci. 41:527 (1987)].

[0022] CRF is involved in psychiatric disorders and neurological diseases including depression and anxiety [D. M. Nielsen, Life Sci. 78:909-919; H. E. Kunzel et al., J. Psychiatr. Res. 37:525-533; D. R. Gehlert et al., Eur. J. Pharmacol. 509:145-153]. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis, as they relate to the dysfunction of CRF neurons in the central nervous system [for a review, see: E. B. De Souze, Hosp. Practice 23:59 (1988)]. Chronic administration of CRF has been shown to produce impairment of the dopamine system suggesting a role in Parkinson's disease [E. Izzo et al., Pharmacol. Biochem. Behav. 81:701-708 (2005)]. Other neurological disorders in which CRF is involved include epilepsy [T. Z. Baram et al., Brain Res. 770:89-95 (1997)] and migraine [T. C. Theoharides et al., Endocrinology 136:5745-5750 (1995)]. CRF has been implicated in alcohol and substance abuse and associated withdrawal symptoms [D. H. Overstreet et al., Pharmacol. Biochem. Behav. 77:405-413; Y. Shaham et al., Psychopharmacology (Berl) 137:184-190]. Moreover, there is evidence that CRF has a role in various endocrine disorders and cardiovascular diseases such as obesity [E. Timofeeva and D. Richard, Neuroendocrinology 66:327-340 (1997)], metabolic syndrome [A. M. Ward et al., Metabolism 53:720-726(2004)], congenital adrenal hyperplasia [D. P. Merke and G. B. Cutler Jr., Endocrinol. Metab. Clin. North Am. 30:121-135 (2001)], Cushing's disease [M. Labeur et al., Curr. Drug Targets Immune Endocr. Metabol. Disord. 4:335-342 (2004)], hypertension [R. J. Briscoe, et al., Brain Res. 881:204-207 (2000)], and stroke [S. L. Stevens et al., J. Cereb. Blood Flow Metab. 23:1151-1159 (2003)]. Gastric disturbances such as irritable bowel syndrome [Y. Tache et al., Eur J. Surg. Sups1:16-22 (2002)] and stress-induced gastric ulceration [K. E. Gabry et al., Mol. Psychiatry 7:474-483, 433 (2002)] have been shown to be related to CRF. In addition, there is indication that CRF has a role in various areas of human female health, for example, premenstrual syndrome [F. Facchinetti et al., Psychosom. Med. 56:418-422 (1994)], infertility [L. Ghizzoni et al., Endocrinology 138:4806-4811 (1997)], sexual dysfunction [J. E. Jones et al., Am. J. Physiol. Regul. Integr. Comp. Physiol. 283:R591-597 (2002)], and premature labor [P. D. Wadhwa et al., Am. J. Obstet. Gynecol. 191:1063-1069 (2004)]. There is also evidence that CRF has a significant role in the immune system indicating therapeutic potential for treating inflammatory disorders [A. Gravanis and A. N. Margioris, Curr. Med. Chem. 12:1503-1512 (2005)], allergies [L. K. Singh et. al., Brain Behav. Immun. 13:225-239 (1999)], multiple sclerosis and other autoimmune disorders [C. Benou et al., J. Immunol. 174:5407-5413 (2005)]. In addition to the preceding, CRF has been implicated in visceral pain [M. Nijsen et al., Neurogastroenterol. Motil. 17: 423-432 (2005)], sleep disorders [T. M. Buckley and A. F. Schatzberg, J. Clin. Endocrinol. Metab. 90:3106-3114(2005)], pituitary tumors or ectopic pituitary-derived tumors [K. D. Dieterich et al., J. Clin. Endocrinol. Metab. 83:3327-3331 (1998)], chronic fatigue syndrome and fibromyalgia [G. Neeck and L. J. Crofford, Rheum. Dis. Clin. North Am. 26: 989-1002 (2000)].

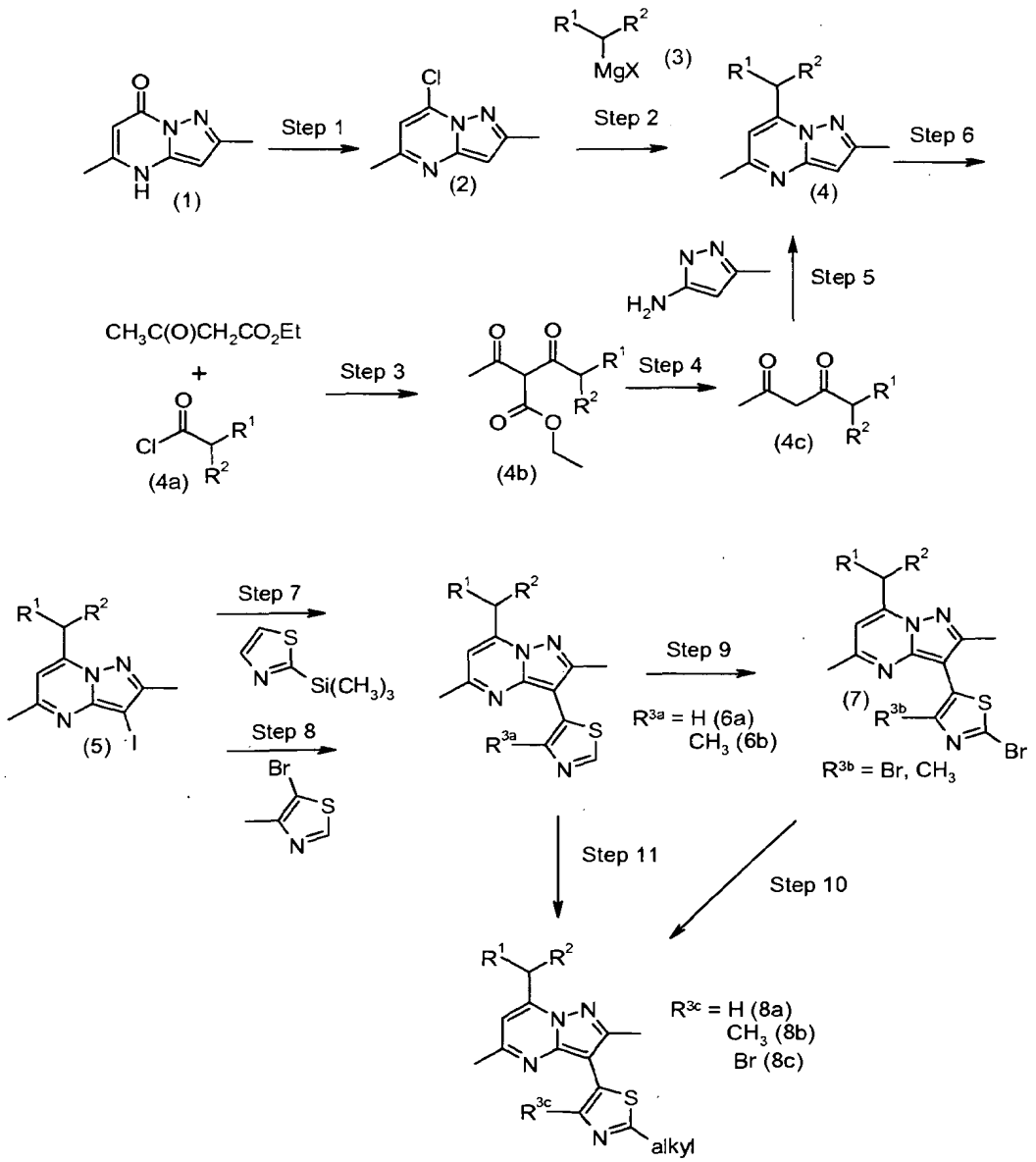
[0023] CRF receptor subtypes, CRF 1 and CRF2, have been identified and are distributed heterogeneously within the brain [D. T. Chalmers et al., TIPS 17:166-72 (1996)] thereby suggesting potential functional diversity [S. C. Heinrichs et al., Regul. Peptides 71:15 (1997)]. For example, widely distributed brain CRF1 receptor are strongly implicated in emotionality accompanying exposure to environmental stressors [G. Liebsch et al., Regul. Peptides 59: 229-39 (1995); D. W. Schulz, PNAS 93: 10477-82 (1996)]. Significantly, CRF1, not CRF2, receptors appear to mediate select anxiogenic like behaviors [Heinrichs et al., 1997]. A more discrete septal/hypothalmic distribution [D. T. Chalmers et al., J. Neurosci. 15(10): 6340-50 (1995)] and the availability of alternative endogenous ligands [J. Vaughan et al., Nature 378: 287-92 (1995)] suggest a different functional role for the CRF2 receptor [Heinrichs et al., 1997]. For example, a novel CRF-

family neuropeptide with preferential affinity for CRF2 relative to CRF1 receptors is reported to suppress appetite without producing the profile of behavioral activation observed with selective CRF1 agonism (H. Tezval et al., PNAS 101(25): 9468-9473 (2004)]. In some cases, CRF2 agonism produces similar effects to those reported for CRF1 antagonists or CRF 1 gene deletion [S. C. Heinrichs, Trends in Pharmacological Sciences 20(8):311-5 (1999)]. For example, while CRF2 agonists have been proposed as antiobesity agents, CRF 1 antagonists may be an important treatment for obesity as well [C. Contoreggi et al., Neuroendocrinology 80(2):111-23 (2004)].

PREPARING COMPOUNDS OF THE INVENTION

[0024] All of the compounds of the present invention can be chemically prepared, for example, by following the synthetic routes set forth below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. For example, the specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare additional compounds of Formula I. The products of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. In the Schemes below all substituents, unless otherwise indicated, are as previously defined and suitable reagents are well known and appreciated in the art.

Scheme 1



[0025] Formation of a compound of formula (6a,b), (7), or 8(a-c) can be carried out in accordance with reactions as depicted in Scheme 1. An appropriate compound of formula (6a,b), (7), or (8a-c) is one in which R^1 and $R^2$are as defined for formula I and R^{3a} = H or CH_3, R^{3b} = Br or CH_3 and R^{3c} = H, CH_3, or Br.

[0026] In Scheme 1, Step 1, the pyrazolo[1,5-a]pyrimidine-7-one of formula (1) is converted to 7-chloro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine using phosphorous oxychloride and dimethylaniline in an inert solvent, such as toluene, at the reflux temperature of the solvent.

[0027] In Step 2, a Grignard reagent of formula (3) (X = Cl or Br) is reacted with the chloride of formula (2), in an inert solvent such as toluene, at reflux temperature to provide the 7-alkyl pyrazolopyrimidine of formula (4).

[0028] Alternatively, a 7-alkyl pyrazolopyrimidine of formula (4) can be obtained as shown in Steps 3, 4, and 5. In Step 3 ethyl acetoacetate is acylated with an acid halide of formula (4a) in the presence of magnesium chloride to provide a diketo-ester of formula (4b). The diketo-ester of formula (4b) is decarboxylated under Krapcho conditions to provide the diketone of formula (4c). For example, (4b) is heated in dimethyl sulfoxide at a temperature of about 130 to 170 °C to perform the decarboxylation. In Step 5, the diketone of formula (4c) is cyclized with 3-amino-5-methylpyrazole to give the 7-alkyl pyrazolopyrimidine of formula (4) in a protic solvent such as methanol, ethanol, or acetic acid. Preferred

conditions use acetic acid at a temperature of about 0 to 60 °C.

[0029] The pyrazolopyrimidine of formula (4) is functionalized to an iodo pyrazolopyrimidine of formula (5) in Step 6 using an excess ofN-iodosuccinimide in acetonitrile.

[0030] In Scheme 1, Step 7 or 8, the iodo pyrazolopyrimidine of formula (5) is reacted with a thiazole zinc halide in a Negishi cross-coupling reaction to provide a thiazolyl pyrazolopyrimidine of formula (6a) or (6b) (Jensen, J.; Skjaerbaek, N.; Vedso, P. Synthesis 2001, 128). The thiazole zinc halide is generated using methods well known to those skilled in the art. For example, in Step 7, 2-trimethylsilanylthiazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by lithium-zinc exchange with $ZnCl_2$. The organozinc reagent is coupled with the iodo pyrazolopyrimidine of formula (5) in the presence of a palladium catalyst, for example, dichloro[1,1'-bis(diphenyl-phosphino)ferrocene]palladium (II) dichloromethane, in an inert solvent, such as THF, at reflux temperature for about 12 to 36 hours, to provide a thiazole pyrazolopyrimidine of formula (6a).

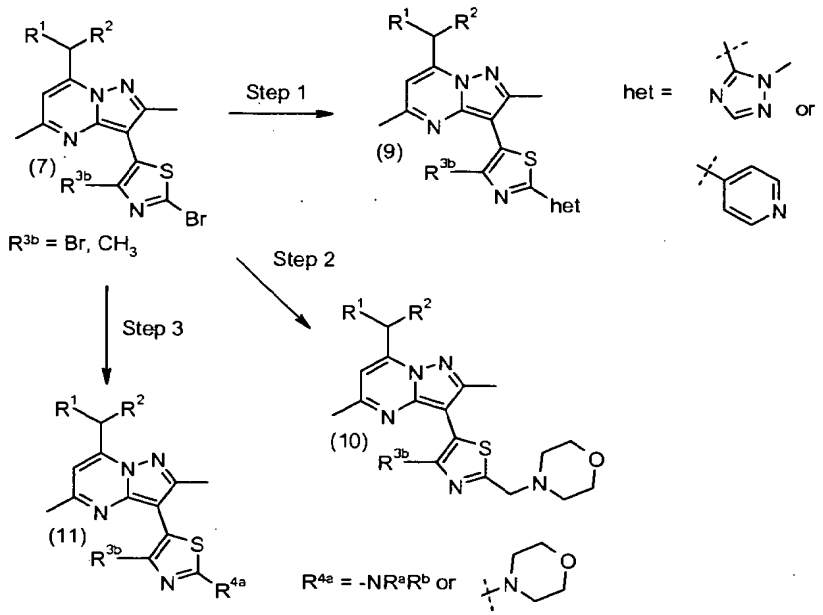
[0031] Alternatively, in Step 8, a thiazole zinc bromide is generated using 5-bromo-4-methylthiazole and zinc metal, and used in the Negishi cross-coupling essentially as described for Step 7, to provide a thiazole pyrazolopyrimidine of formula (6b).

[0032] In Scheme 1, Step 9, a thiazole of formula (6a,b) is brominated to give a bromo or dibromo thiazole of formula (7), wherein R^{3b} = Br or CH_3. The thiazole is brominated with either 1 or 2 eq of N-bromosuccinimide, depending on whether R^{3a} is CH_3 or H, respectively.

[0033] An alkyl thiazole of formula (8a-c) is obtained from either a thiazole of formula (6a,b) in Step 11, or from a bromothiazole of formula (7) in Step 10. In Step 10, halogen-lithium exchange with *n*-, *sec*-, or *t*-butyl lithium provides a thiazole lithium reagent, which is subsequently reacted with electrophiles, such as alkylhalides, like iodomethyl methylether or iodobutane. In Step 11, the thiazole lithium reagent is formed via deprotonation using *n*-, *sec*-, or *tert*-butyl lithium and then subsequently reacted with an electrophile, like iodomethyl methylether or iodobutane.

[0034] It will be appreciated by one skilled in the art that the thiazole ring system is readily functionalized and that thiazole intermediates such as 2-trimethylsilanyl-thiazole (Dondoni, A.; et. al. J. Org. Chem. 1988, 53, 1748) can be readily prepared. 5-Bromo-4-methylthiazole is obtained by bromination of 4-methylthiazole with bromine in acetic acid (Collins, I. J., et. al. WO2003093252, 13 Nov 2003). 2,5-Dimethyl-4*H*-pyrazolo[1,5-a]pyrimidine-7-one (1) is readily prepared by condensation of ethyl acetoacetate and 5-methyl-2H-pyrazol-3-ylamine in refluxing acetic acid.

Scheme 2



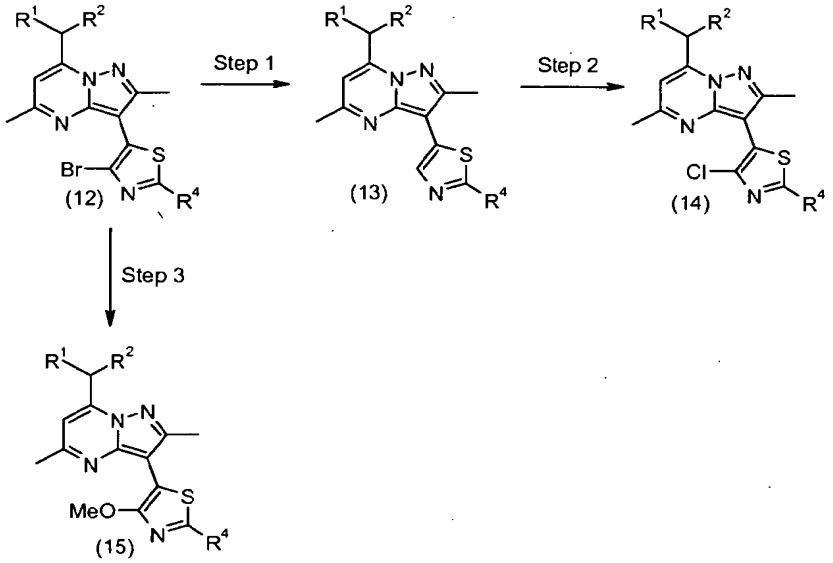
[0035] Formation of a compound of formula (9), (10), or (11) can be carried out in accordance with reactions as depicted in Scheme 2. An appropriate compound of formula (9), (10), or (11) is one in which R^1, R^2, R^a, and R^b are as defined for formula I and R^{3b} = Br or CH_3, and R^{4a} = $-NR^aR^b$ or -N-morpholinyl and "het" is defined as depicted.

[0036] In Step 1, a bromothiazole of formula (7) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (9). For example, 1-methyl-1,2,4-triazole is treated with *n*-, *sec*-, or *tert*-butyl lithium, followed by zinc chloride, at about -80 to -65 °C, and reacted *in situ* with a bromothiazole of formula (7). The reaction is performed preferentially in an inert solvent, such as THF, in the presence of a palladium catalyst, such as dichloro[1,1'-bis(diphenyl-phosphino)ferrocene]palladium (II) dichloromethane or tetrakis(triphenylphosphine) palladium (0). The reaction is warmed to reflux temperature. Alternatively, the heterocyclic zinc reagent is formed from a haloheterocycle, such as 4-iodopyridine and zinc metal.

[0037] In Scheme 2, Step 2, an intermediate 2-formyl thiazole is formed via halogen-lithium exchange using *n*-, *sec*-, or *t*-butyl lithium followed by reaction with N-formyl morpholine. The formyl thiazole is subjected to a reductive amination in the presence of an organic amine, such as morpholine, to provide a morpholinyl methyl thiazole of formula (10). Reductive aminations are well-known in the art typically using an inorganic borohydride reagent such as sodium borohydride or sodium cyanoborohydride. Preferred conditions use sodium triacetoxyborohydride in an inert solvent such as dichloromethane or THF.

[0038] In Step 3, a bromothiazole of formula (7) undergoes a displacement reaction with an amine of formula $-NR^3R^b$ or with morpholine to provide an aminothiazole of formula (11). The reaction is preformed in an inert solvent, such as THF or dioxane, using an inorganic base, such as cesium carbonate at 70 to 110 °C.

Scheme 3

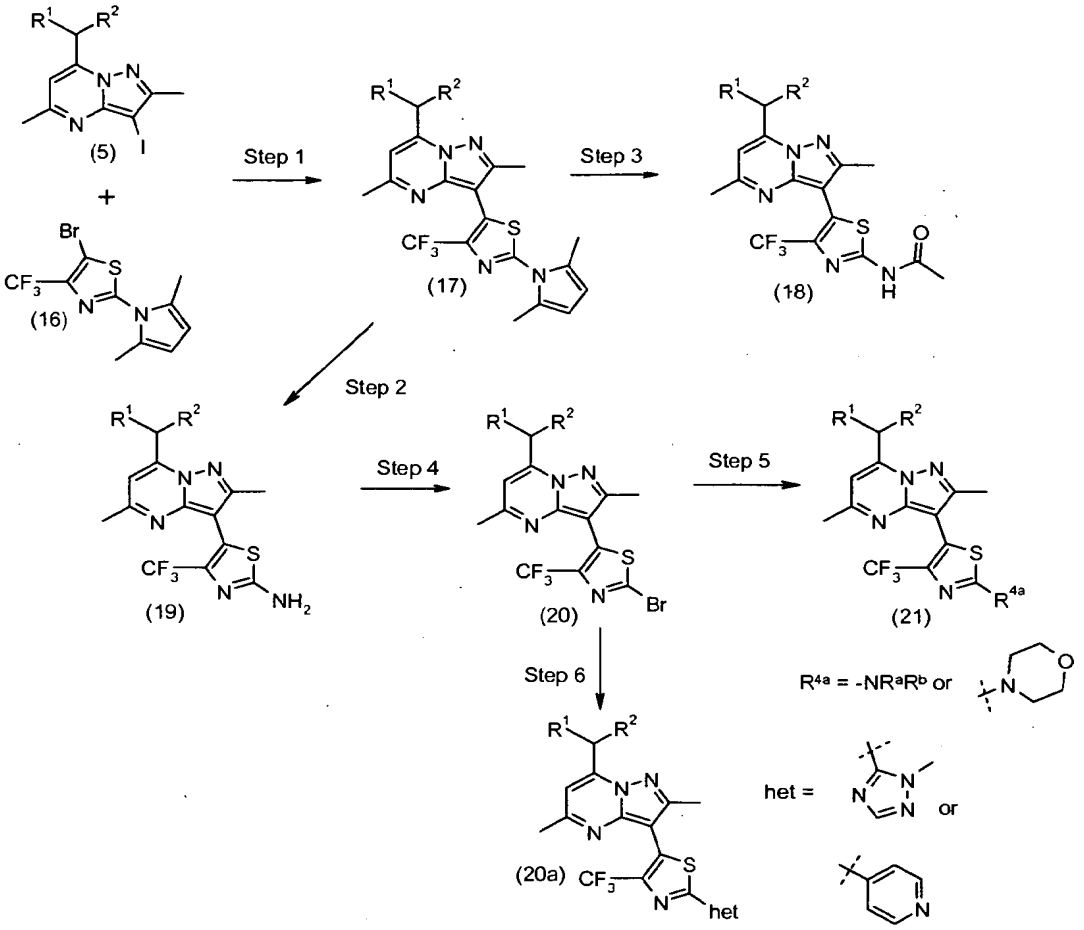


[0039] Formation of a compound of formula (13), (14), or (15) can be carried out in accordance with reactions as depicted in Scheme 3. An appropriate compound of formula (13), (14), or (15) is one in which R^1, R^2, and R^4 are as defined for formula I.

[0040] It will be recognized by one skilled in the art that a 4-bromothiazole, such as that of formula (12) is readily manipulated to other functionality. For example, in Step 1, the bromide can be dehalogenated with cuprous chloride to give a thiazole of formula (13) which is subsequently chlorinated with N-chlorosuccinimide to provide a 4-chlorothiazole of formula (14).

[0041] In Scheme 3, Step 3, a 4-bromothiazole of formula (12) is displaced with sodium methoxide in the presence of copper (I) iodide in methanol at about 100 to 120 °C in an inert solvent such as dimethylformamide, to provide a 4-methoxy thiazole of formula (15).

Scheme 4



[0042] Formation of a compound of formula (17), (18), (19), (20), (20a), or (21) can be carried out in accordance with reactions as depicted in Scheme 4. An appropriate compound of formula (17), (18), (19), (20), (20a), or (21) is one in which R^1, R^2, R^a, and R^b are as defined for formula I and R^{4a} is $-NR^aR^b$ or-N-morpholinyl and "het" is defined as depicted.

[0043] In Scheme 4, Step 1, an iodopyrazolopyrimidine of formula (5) and a 5-bromothiazole of formula (16) undergo a Negishi cross-coupling to form a dimethylpyrrolylthiazole of formula (17). For example, the 5-bromothiazole of formula (16) is treated with *n*-, *sec*-, or *tert*-butyl lithium and then with zinc chloride at about -80 to -65 °C. The organozinc reagent is reacted *in situ* with an iodopyrazolopyrimidine of formula (5). The coupling reaction is performed preferentially in an inert solvent, such as THF, at reflux temperature, in the presence of a palladium catalyst, such as bis(tri-*t*-butylphosphine) palladium (0).

[0044] In Step 2, a dimethylpyrrolylthiazole of formula (17) is deprotected to provide an aminothiazole of formula (19). The dimethylpyrrole is treated with hydroxylamine in acetic acid at a temperature of about 60 to 100 °C, for about 4 to 8 h, preferably for about 6 h. In Step 3, to form the thiazole acetamide of formula (18), the same conditions are used as in Step 2, with the exception that the reaction is continued for about 72 h.

[0045] In Scheme 4, Step 4, a 2-aminothiazole of formula (19) is converted to a 2-bromothiazole of formula (20) using a modified Sandmeyer reaction. Preferred conditions use an alkylnitrite, such as *t*-butylnitrite, and copper (II) bromide, in acetonitrile at a temperature of about 60 to 80 °C.

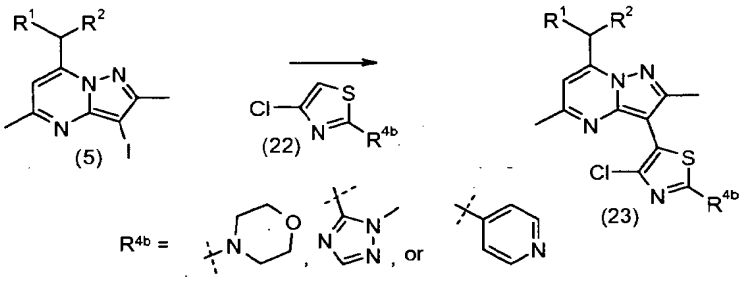
[0046] In Step 5, a 2-bromothiazole of formula (20) undergoes a displacement reaction with an amine of formula $-NR^aR^b$ or with morpholine to provide an aminothiazole of formula (21). The reaction is performed in an inert solvent, such as methanol, THF, or dioxane, or is treated neat, with an excess of the amine at a temperature of about 70 to 110 °C. Alternatively the reaction is performed with the reacting amine and an excess of triethylamine, or an inorganic base, such as cesium carbonate. Also contemplated in the synthesis of aminothiazoles of formula (21) are various deprotection steps, such as removal of a *tert*-butyl ester carbamic acid (BOC), as may be required or beneficial for carrying out the

reactions above wherein -NR^aR^b carries additional amine functionality as defined for formula I. The selection and use of suitable protecting groups is well known and appreciated in the art (see for example, Protecting Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience)).

[0047] In Scheme 4, Step 6, a 2-bromothiazole of formula (20) is coupled with a heterocyclic zinc reagent in a Negishi cross-coupling reaction to provide a thiazole heterocycle of formula (20a) in a manner similar to that as described for Scheme 2, Step 1.

[0048] It will be appreciated by the skilled artisan that a functionalized thiazole of formula (16) can be prepared by means known in the art. For example, cyclization of thiourea with a bromoketone, such as 3-bromo-1,1,1-trifluoropropan-2-one, provides 4-trifluoromethyl-thiazole-2-ylamine. Subsequent bromination and protection of the amine using hexane-2,5-dione provides (16).

Scheme 5

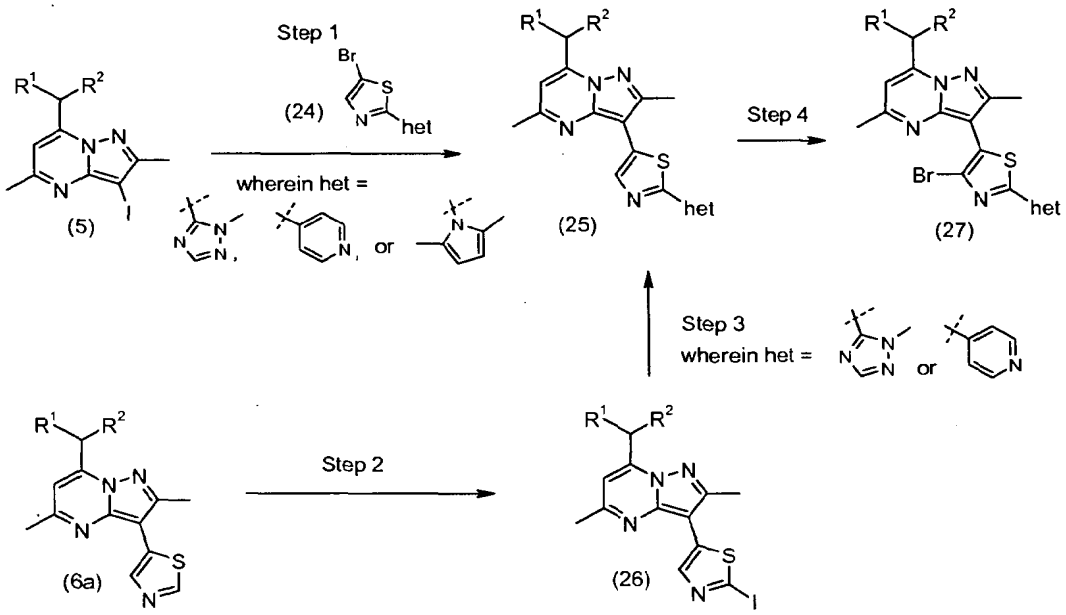


[0049] Formation of a compound of formula (23) can be carried out in accordance with reactions as depicted in Scheme 5. An appropriate compound of formula (23) is one in which R^1 and R^2 are as defined for formula I and R^{4b} is defined as depicted.

[0050] An iodopyrazolopyrimidine of formula (5) and a 4-chloro-2-morpholino-thiazole, for example, of formula (22) undergo cross-coupling to form a pyrazolopyrimidine thiazole of formula (23). For example, the reactants are coupled in the presence of copper iodide, palladium acetate, and triphenylphosphine, with a base such as cesium carbonate. The coupling reaction is performed preferentially in an inert solvent, such as DMF, at about 100 - 150 °C. for 4 - 24 h.

[0051] It will be appreciated by the skilled artisan that a functionalized thiazole of formula (22) can be prepared by means known in the art. For example, 2,4-dichlorothiazole can be reacted with morpholine to give the 2-morpholino-thiazole of formula (22). 2,4-Dichlorothiazole can also be exhaustively brominated to provide 2,5-dibromo-4-chlorothiazole. Subsequent bromine-lithium exchange with *n*-butyl lithium in THF at -90 °C and quench with water provides 2-bromo-4-chlorothiazole [J. Chem. Soc. Perkin Trans 1: Org Bioorg. Chem. (1972-1999), (2):215-219 (1992)]. 2-Bromo-4-chlorothiazole can be subjected to a Negishi cross-coupling reaction with a heterocyclic zinc reagent to obtain the thiazol-2-yl triazole or pyridine.

Scheme 6



[0052] Formation of a compound of formula (27) can be carried out in accordance with reactions as depicted in Scheme 6. An appropriate compound of formula (27) is one in which R^1 and R^2 are as defined for formula I and "het" is defined as depicted for Step 1 or Step 3, respectively.

[0053] In Scheme 6, Step 1, a heterocyclic thiazole, for example, of formula (25) is obtained by reaction of an iodopyrazolopyrimidine of formula (5) with a bromothiazole of formula (24). The reaction is performed in the presence of N-butylammonium bromide and a base, such as potassium acetate with a palladium catalyst such as palladium acetate with tris(2,4-di-*tert*-butyl-phenyl)-phosphane, in an inert solvent such as N-methylpyrrolidinone at a temperature of about 100 - 150 °C.

[0054] Alternatively, in Step 2, a thiazolyl pyrazolopyrimidine of formula (6a) is iodinated to provide a 2-iodothiazole of formula (26). The thiazole is treated with lithium diisopropylamide at a temperature of -70 to -80 °C for about one hour and then treated with N-iodosuccinimide at about the same temperature in an inert solvent, such as THF. This is followed by Step 3, wherein a triazolyl or 4-pyridyl thiazole of formula (25) is formed using Negishi cross-coupling conditions similar to those described for Scheme 2, Step 1.

[0055] In Scheme 6, Step 4, a thiazolyl pyrazolopyrimidine of formula (25) is brominated to give a bromothiazole of formula (27). The bromination is effected using N-bromosuccinimide in the presence of a small amount of acetic acid in an inert solvent, such as acetonitrile.

[0056] A compound of formula (27), wherein het = 2,5-dimethyl-pyrrol-1-yl, can be further elaborated to obtain compounds of the invention as described in Scheme 4, Steps 2, 3, 4, and 5.

[0057] It will be appreciated by the skilled artisan that heterocycle thiazoles of formula (24) can be readily prepared by means known in the art. For example, thiazole-2-carboxylic acid amide can be cyclized to the triazole with 1,1-dimethoxy-N,N-dimethyl-methanamine, followed by N-methyl-hydrazine to obtain the triazolyl thiazole, which can be subsequently brominated with N-bromosuccinimide. Literature procedures afford 4-thiazol-2-yl-pyridine which can be brominated to provide 4-(5-bromo-thiazol-2-yl)-pyridine. 5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-thiazole can be readily obtained by reaction of 2-amino-5-bromothiazole with hexane-2,5-dione.

[0058] As used herein, "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "LC/MS" refers to liquid chromatography/mass spectrometry; "GC/MS" refers to gas chromatography/mass spectrometry"; "HR-ToF' refers to high resolution time-of-flight; "APCI" refers to atmospheric pressure chemical ionization; "8" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "EtOAc" refers to ethyl acetate; "MeOH" refers to methanol; "EtOH" refers to ethanol; "DMF" refers to dimethylformamide.

EXAMPLES

[0059] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following preparations and examples are provided to describe the invention

in further detail. The reagents and starting materials are readily available to, or may be readily synthesized by, one of ordinary skill in the art. Examples 1-35 provide representative compounds and illustrate the preparation thereof. Examples A-D illustrates various biological assays that can be used for determining the biological properties of the compounds of the inventions. Those skilled in the art will promptly recognize appropriate variations from the procedures described in the examples. The names of the compounds of the present invention are provided by ChemDraw Ultra® version 7.0.1. Salts are named as the free base plus the conjugate acid.

Preparation 1

2,5-Dimethyl-4H-pyrazolo[1,5-*a*]pyrimidin-7-one

[0060] Add ethyl acetoacetate (128 g, 0.98 mol) dropwise to an acetic acid solution (500 mL) of 5-methyl-2*H*-pyrazol-3-ylamine (100 g, 0.95 mol), keeping the temperature at 25-28 °C. Heat the mixture at reflux for 10 h and then cool to room temperature. Add the reaction to *tert*-butyl methyl ether (5 L) cooled to 5 °C, keeping the temperature below 10 °C. Stir for 1 h at 5 °C, and filter. Dry the resulting material *in vacuo* overnight to provide a white solid (158 g, 96%).

Preparation 2

7-Chloro-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0061] To a suspension of 2,5-dimethyl-4*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (10.0 g, 61.3 mmol) in toluene (150 mL) add *N*,*N*-dimethylaniline (9.7 mL, 76.7 mmol). Add phosphorus oxychloride (11.2 mL, 122.6 mmol) dropwise to this white suspension. Reflux for 3 h under an inert atmosphere, cool to room temperature, and concentrate the reaction to a brown oil using reduced pressure. Dissolve the oil in ethyl acetate (250 mL) and basify with 1.0 N NaOH. Separate the organic phase and extract the basic aqueous phase with ethyl acetate (2 × 100 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a brown solid. Purify the material using flash chromatography, eluting with 80% hexane/20% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 20% increments to provide a light green solid (6.65 g, 59%). ES/MS m/z (^{35}Cl) 182.3 $(M+1)^+$.

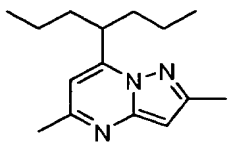
Alternate Procedure:

[0062] Add 2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-7-one (20 g, 122 mmol) to 1,4-dioxane (60 mL). Stir the mixture at 22 °C for 10 min and then add N,N-diethylaniline (20.8 mL, 128 mmol). Stir for an additional 5 min and then add phosphorus oxychloride (11.7 mL, 126 mmol) over 15 min. Stir the mixture at 22 °C for 15 min, then heat to 80-85 °C over 35 min and hold the reaction at this temperature for 1.5 h. Add the cooled reaction mixture slowly to a solution of potassium phosphate dibasic (106.7 g, 612.82 mmol) in water (325 mL) cooled to 0-5 °C, keeping the temperature below 5 °C during the addition. Stir the mixture at 22 °C and then add methyl-*t*-butyl ether (150 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by silica gel chromatography, eluting with hexanes/ethyl acetate (2/1) to provide the title compound as a yellow solid (20.7 g, 88%). ES/MS m/z (^{35}Cl) 182 $(M+1)^+$.

Preparation 3

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0063]



[0064] Charge an oven dried flask equipped with a reflux condenser, with anhydrous THF (40 mL), iodine (catalytic amount), magnesium ribbon (1.92 g, 78.9 mmol) and 4-bromoheptane (9.4 mL, 52 mmol). Heat the reaction to reflux in an oil bath. The temperature of the reaction spikes as the Grignard reaction is initiated. Stir the reaction an additional 4 h at 90 °C and cool to room temperature. Allow the magnesium metal to settle out (can also be centrifuged) and canulate

off the Grignard reagent under positive argon pressure into a flask charged with 7-chloro-2,5-dimethylpyrazolo [1,5-*a*] pyrimidine (4.80 g, 26.3 mmol) in anhydrous toluene (20 mL). Reflux the reaction under an inert atmosphere overnight. Cool the reaction to room temperature and quench with water. Dilute with ethyl acetate (150 mL), then add water (100 mL) and saturated ammonium chloride (50 mL). Separate and extract the aqueous phase with dichloromethane (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 80% hexane/20% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 20% increments to give yellow crystals (3.08 g, 48%). ES/MS m/z 246.3 $(M+1)^+$.

Alternate Procedure:

[0065] Heat a mixture of magnesium turnings (3.5 g, 144 mmol) and a catalytic amount of iodine (100 mg) in THF (100 mL) to 65 °C under a nitrogen atmosphere. Add a few drops of neat 4-bromoheptane and heat the mixture until the reaction starts. Then add a solution of 4-bromoheptane (17.6 mL, 94.9 mmol) in THF (42 mL) keeping the temperature at 65-70 °C over 2 h. Reflux the mixture for an additional hour and then cool the reaction to 22 °C. Add the prepared Grignard reagent to a solution of 7-chloro-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (10.2 g; 53.3 mmol) in THF (60 mL) cooled to 0 °C under a nitrogen atmosphere. Add the magnesium reagent solution via cannula over 45 min while keeping the temperature below 10 °C. Then stir the mixture for an additional 30 min at 5 °C. Add to this mixture a 10% aqueous ammonium chloride solution (wt/wt) (125 mL) and stir at 22 °C for 30 min. Separate the organic layer and extract the aqueous layer with ethyl acetate (2 × 25 mL). Combine the organic layers and dry over sodium sulfate. Filter the mixture and evaporate the solvent. Purify the crude material by silica gel flash chromatography using an eluent of hexanes/ethyl acetate (5/1) to provide the title compound (8 g, 62%). ES/MS m/z 246 $(M+1)^+$.

Preparation 3a

7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

Alternate Route

Step 1: 3-Acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester

[0066] Add magnesium chloride (14.63 g, 153.70 mmol) to dichloromethane (500 mL) followed by addition of ethyl acetoacetate (19.55 mL, 20.00 g, 153.79 mmol) all at once and stir at room temperature for one hour. Cool the mixture in an ice water bath and and add pyridine (24.86 mL, 24.32 g, 307.39 mmol) dropwise. Add di-n-propylacetyl chloride (25.00 g, 153.70 mmoles) dropwise at 0 °C under nitrogen to the white slurry. After the addition is complete remove the cooling bath, warm to ambient temperature, and stir for 16 h. Quench the reaction with 1 N HCl (400 mL) and separate the bottom layer. Dry the organic portion over magnesium sulfate, filter, and concentrate under vacuum to give a yellow oil (34 g, 86%). Use the material directly in the next step without further purification.

Step 2: 5-Propyl-octane-2,4-dione

[0067] Dissolve 3-acetyl-3-oxo-4-propyl-heptanoic acid ethyl ester (32.4 g, 126.39 mmoles) in dimethyl sulfoxide (100 mL) and water (5 mL). Heat the solution at 150 °C for 6 to 8 h or follow the reaction by GC/MS. Cool the reaction and extract with heptane (3 × 100 mL). Wash the combined organic portions with water (100 mL) and brine (100 mL). Concentrate under vacuum at 50 °C to remove most of the heptane. Obtain 23.29g of an oil and use directly in the next step.

Step 3: 7-(1-Propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0068] Mix 5-propyl-octane-2,4-dione (15 g, 81.40 mmoles) in acetic acid (15 mL) and cool in an ice bath. Add 5-amino-3-methylpyrazole (7.91 g, 81.40 mmol) portionwise and stir at ambient temperature. Check for completion of the reaction by GC/MS after 3 h. GC indicates correct region isomer in comparison with an authentic sample. Distill off the excess acetic acid. Add water (50 mL) and extract with heptane (50 mL). Wash the heptane with brine (50 mL). Dry the organic layer over $MgSO_4$, filter, and concentrate under vacuum to give a crude oil (15.8 g, 79%). ^1H NMR ($CDCl_3$): 6.39 (s, 1H); 6.31 (s, 1H); 3.75 (m, 1H); 2.55 (s, 3H); 2.45 (s, 3H); 1.71 (q, 4H); 1.23 (m, 4H); 0.85 (t, 6H).

[0069] Prepare the following compound essentially as described in Preparation 3, using either procedure. Use 3-bromopentane to prepare the Grignard reagent.

Prep. No.	Chemical name	Physical data
4	7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	ES/MS m/z 218.1 $(M+1)^+$

Preparation 5

7-(1-Propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidine

[0070] Dissolve 7-(1-propyl-butyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (3.08 g, 12.5 mmol) in anhydrous acetonitrile (25 mL) and add 6 portions (0.70 g each) ofN-iodosuccinimide (4.2 g, 18.7 mmol) at 10 minute intervals. Stir over the weekend at room temperature. Strip off the acetonitrile and dilute the oil with dichloromethane (100 mL). Wash with saturated ammonium chloride solution (2 × 50 mL). Collect the organic phase, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure to yield a dark red oil. Purify the oil using flash chromatography, eluting with 100% hexane/0% (20% ethyl acetate/hexane) to 0% hexane/100% (20% ethyl acetate/hexane) in a step gradient of 50% increments to give an orange oil (10.97 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): 6.42 (s, 1H), 3.74-3.70 (m, 1H), 2.58 (s, 3H), 2.46 (s, 3H), 1.74-1.68 (m, 4H), 1.28-1.14 (m, 4H), 0.84 (t, J = 7.0 Hz, 6H).

[0071] Prepare the compound below essentially as described in Preparation 5.

Prep. No.	Chemical name	Physical data
6	7-(1-Ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-*a*]pyrimidine dimethyl-pyrazolo[1,5-*a*] pyrimidine	1H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.59 (m, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.86-1.76 (m, 4H), 0.85 (t, J = 7.5 Hz, 6H).

Alternate procedure for Preparation 6:

[0072] Add acetic acid (1 mL) and N-iodosuccinimide (6.7 g, 29.9 mmol) in one portion to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (6 g, 27.5 mmol) in acetonitrile (60 mL). Stir the mixture at 22 °C for 2 h. Evaporate the solvent and take the residue up in water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (9.2 g, 96%). ES/MS m/z 344 $(M+1)^+$.

Preparation 7

2-Trimethylsilanyl-thiazole

[0073] Mix n-butyl lithium (20.4 mL, 51.0 mmol, 2.5 M in hexane) with diethyl ether (50 mL) in a three-necked flask, equipped with a dropping funnel and thermometer. Cool to -78 °C and add dropwise a solution of thiazole (4.25 g, 50.0 mmol) in diethyl ether (50 mL). After the addition is complete, stir the reaction mixture at -78 °C for 30 min, followed by addition of chlorotrimethylsilane (5.4 g, 50 .0 mmol). Stir at -78 °C for an hour and then warm to room temperature. Quench the reaction by adding saturated sodium bicarbonate. Extract the aqueous layer with diethyl ether. Wash the combined organic portions with brine and dry over sodium sulfate. Filter and concentrate under reduced pressure to give a residue. Purify by distillation to give 8.33 g (52-56 °C/ 15 mm Hg) of title compound. ^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, 1H, J=2.6 Hz), 7.54 (d, 1H, J = 2.6 Hz), 0.43 (s, 9H).

Preparation 8

5-Bromo-4-methylthiazole

[0074] Add bromine (9.27 mL, 182 mmol) to a solution of 4-methylthiazole (15.0 g, 152 mmol) in acetic acid (30 mL) at 0 °C. Slowly warm the reaction mixture to room temperature and stir overnight. Dilute with dichloromethane and wash with 1 N NaOH and brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum. Purify the crude product by silica gel column chromatography, elueting with hexanes/ethyl acetate (5/1) to obtain the title compound (9.94 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 2.43 (s, 3H).

Preparation 9

Thiazole-2-carboxylic acid ethyl ester

[0075] To a mixture of 2-trimethylsilylthiazole (135 g, 858.1 mmol) in toluene (1350 mL) add a solution of ethyl chloroformate (98.4 mL, 1.03 mol) in toluene (1350 mL) over 15 min. Stir the reaction at 22 °C for 2 h. Add the solution over aqueous sodium carbonate 25% (wt/wt) (5 L) and stir for 30 min. Separate the organic layer and re-extract the aqueous layer with methylene chloride (2 × 1 L). Combine the organic layers and evaporate the solvent to provide the title compound (134 g, 99%). ES/MS m/z 158 $(M+1)^+$.

Preparation 10

Thiazole-2-carboxylic acid amide

[0076] Add thiazole-2-carboxylic acid ethyl ester (150 g, 0.9 mol) to a mixture of methanol (75 mL) and 30% aqueous ammonium hydroxide (750 mL) and heat the mixture at reflux for 1 h. Then cool to 22 °C and evaporate the methanol under vacuum. Stir the mixture for 30 min at room temperature and filter the solid. Dry the isolated solid under vacuum to afford the title compound (98 g, 85%). ES/MS m/z 129 $(M+1)^+$.

Preparation 11

1-Methyl-5-thiazol-2-yl-1H-[1,2,4]triazole

[0077] Cool 1,1-dimethoxy-*N*,*N*-dimethyl-methanamine (240 mL) to 10 °C and add thiazole-2-carboxylic acid amide (60 g, 421 mmol) in three portions. Stir the mixture at 10 °C for 30 min. Then heat the mixture gradually to reflux in 45 min. Distill off the methanol formed and then heat the reaction to 100 °C for 1.5 h. Cool the mixture to 60 °C and remove the excess 1,1-dimethoxy-N,N-dimethyl-methanamine by vacuum distillation. Cool the residue to 22 °C and add hexanes (200 mL). Triturate the mixture for 15 min, filter, and dry the solid to constant weight before using in the next step.

[0078] Add the solid isolated above (68 g) to acetic acid (680 mL) and cool the mixture to 10 °C. Add *N*-methylhydrazine (27 mL, 509 mmol) at such a rate as to keep the temperature below 15°C. Warm the mixture to 20 °C in 30 min and then heat gradually to 90 °C. Stir at 90 °C for 30 min and then cool to 22 °C. Remove the acetic acid by vacuum distillation. Add the residue over water and adjust to pH = 8 by adding 25% aqueous sodium hydroxide solution. Extract the aqueous layer with methyl-*t*-butyl ether (3 × 600 mL). Combine the organic layers and evaporate the solvent. Purify the resulting residue by silica gel chromatography using an eluent of hexanes/isopropanol (9/1) to provide the title compound (49 g, 70%). ES/MS m/z 167 $(M+1)^+$.

Preparation 12

5-(5-Bromo-thiazol-2-yl)-1-methyl-1*H*-[1,2,4]thiazole

[0079] To a mixture of methyl-5-thiazol-2-yl-1H-[1,2,4]triazole (6.55 g; 39.4 mmol) and dimethylformamide (32 mL), add N-bromosuccinimide (14 g, 78.8 mmol) in three portions over 1 h. Stir the mixture at 22 °C for 18 h and then add to water (300 mL) chilled to 0-5 °C. Separate the aqueous layer and extract with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic layers and wash with 7% aqueous sodium hydrogen carbonate (100 mL) and then dry over sodium sulfate. Filter and evaporate the solvent to afford the title compound (9.5 g, 93%). ES/MS m/z $^{79}Br/^{81}Br$) 245/247 $(M+1)^+$.

Preparation 13

2,5-Dimethyl-3-[2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine

[0080] Combine 5-(5-bromo-thiazol-2-yl)-1-methyl-1H-[1,2,4]triazole (6.5 g, 23.8 mmol) and 2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*]pyrimidine (6 g, 24.5 mmol) in N-methylpyrrolidinone (58 mL) and stir to complete solution under nitrogen. Then add tetra-N-butylammonium bromide (5.47 g, 16.7 mmol) and potassium acetate (11.8 g, 119 mmol) and heat the mixture to 100 °C under a nitrogen atmosphere. Degas the hot mixture by three cycles of vacuum/nitrogen purge. Then add palladium acetate (216 mg, 0.94 mmol) and tris(2,4-di-*tert*-butyl-phenyl)-phosphane (787 mg, 1.2 mmol). Heat the mixture 4 h at 125 °C under nitrogen. Cool the mixture to 22 °C and add to water (750 mL). Extract the aqueous layer with methyl-*t*-butyl ether (3 × 200 mL), combine the organic portions, and evaporate. Purify the residue by filtration through a silica gel pad eluting with hexanes/ethyl acetate (4/1). Combine the product containing fractions

and evaporate the solvent to afford the title compound (7 g, 72%). ES/MS m/z 410 $(M+1)^+$.

Preparation 14

2,5-Dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine

[0081] Charge an oven dried flask with 2-trimethylsilanylthiazole (1.765 g, 11.24 mmol) dissolved in anhydrous THF (30 mL) and chill under an inert atmosphere to -78 °C. Slowly add n-butyl lithium (2.5 M hexane solution, 4.5 mL, 11.24 mmol) and stir 30 min at -78 °C. Add anhydrous zinc chloride (2.26 g, 16.58 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to rise to room temperature, stir 30 min, and add 7-(1-propyl-butyl)-3-iodo-2,5-dimethyl-pyrazolo [1,5-*a*] pyrimidine (1.624 g, 5.18 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.423 g, 0.518 mmol). Reflux overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with saturated sodium bicarbonate, and dilute with ethyl acetate (150 mL). Separate and extract the aqueous with ethyl acetate (75 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/ 0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient of 10% increments to give a white solid (0.720 g, 42%). ES/MS m/z 329.0 $(M+1)^+$.

[0082] Prepare the compound below essentially as described in Preparation 14.

Prep. No.	Chemical name	Physical data
15	7-(1-Ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-*a*]pyrimidine	1H NMR (400 MHz, $CDCl_3$): d 8.75 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.47 (s, 1H), 3.62-3.55 (m, 1H), 2.65 (s, 3H), 2.61 (s, 3H), 1.89-1.75 (m, 4H), 0.85 (t, 6H, J = 7.5 Hz), 0.85 (t, 6H, J = 7.5 Hz).

Alternate procedure for Preparation 15:

[0083] Add n-butyl lithium (76.5 mL, 191 mmol, 2.5 M in hexanes) to a solution of 2-trimethylsilylthiazole (30 g, 191 mmol) in THF (450 mL) at -78 °C under nitrogen, keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for 30 min and then add zinc chloride, dry powder, (39.9 g, 286 mmol) in one portion and warm the mixture to 22 °C over one hour. Add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, (30 g, 87 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride (6.5 g, 8 mmol) and heat the mixture to reflux under nitrogen for 8 h. Cool the mixture to 22 °C and add 10% aqueous ammonium chloride (450 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2 × 100 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent to afford the title compound (20.4 g, 78%). ES/MS m/z 301 $(M+1)^+$.

Preparation 16

7-(1-Ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0084] Add a freshly prepared solution of lithium di-*i*-propylamide (150 ml; 62.4 mmol, 0.6 M in THF) to a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-*a*]pyrimidine, (17.8 g, 62.4 mmol) in THF (100 mL) at -78 °C under a nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Stir the mixture at -78 °C for one hour and then add a solution ofN-iodosuccinimide (15 g, 63 mmol) in THF (100 mL) keeping temperature below -74 °C. Warm the reaction gradually to 22 °C and then add a 10% aqueous solution of ammonium chloride (300 mL). Separate the organic layer and wash the aqueous layer with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic layers, dry over sodium sulfate, filter, and evaporate the solvent. Purify the resulting residue by silica gel chromatography, eluting with hexanes/acetone (5/1) to afford the title compound (15 g, 60%). ES/MS m/z 427 $(M+1)^+$.

Example 1

7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-thiazol-5-yl)-pyrazolo[1,5-*a*]pyrimidine

[0085] Add Rieke® zinc (10 g in 100 mL of THF, 13.2 mL, 18.48 mmol) to 5-bromo-4-methylthiazole (2.13 g, 18.48 mmol) and heat at reflux for 2 h. Cool the mixture to room temperature and settle the zinc down by centrifuge. Bubble nitrogen gas through 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (900 mg, 2.62 mmol) in dry tet-

rahydrofuran (10 mL) and add the organozinc bromide solution followed by addition of [1,1'-bis(diphenylphosphino) ferrocene]-dichloropalladium(II) (106 mg, 0.13 mmol). Stir the reaction mixture under reflux overnight and cool to room temperature. Add ammonium chloride solution to the reaction mixture and extract with dichloromethane. Dry the organic portion over sodium sulfate, filter, and remove the solvent under vacuum. Purify the crude product by silica gel column chromatography, elueting with hexane/ethyl acetate (3/1) to obtain the title compound (652 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 6.48 (s, 1H), 3.63 (m, 1H), 2.57 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.85 (m, 4H), 0.90 (t, 6H, J = 7.3Hz). ES/MS m/z 315 $(M+1)^+$.

Preparation 17

3-(2,4-dibromo-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0086] Dissolve 2,5-dimethyl-7-(1-propyl-butyl)-3-thiazol-5-yl-pyrazolo[1,5-*a*] pyrimidine (3.15 g, 9.59 mmol) in acetonitrile (100 mL) and add N-bromosuccinimide (4.27 g, 24.0 mmol) in one aliquot. Stir overnight under an inert atmosphere and confirm the reaction is complete using TLC. Concentrate under reduced pressure, dilute the oil with dichloromethane (150 mL), and wash with water (75 mL). Dry the organic phase over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting oil using flash chromatography, eluting with 100% hexane/0% (30% THF/hexane) to 0% hexane/100% (30% THF/hexane) in a step gradient (0-10-15-20-25-30-35-40-45-50-100% of 30% THF/hexane) to give yellow crystals (3.70 g, 79%). ES/MS m/z (^{79}Br^{81}Br) 486.7 $(M+1)^+$.

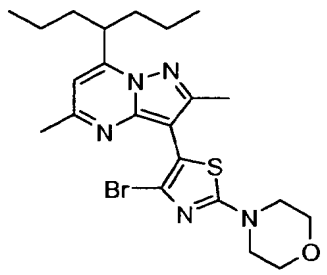
[0087] Prepare the compounds below essentially as described in Preparation 17, with the exception that dichloromethane is used as the solvent.

Ex. No.	Chemical name	Physical data
2	3-(2,4-Dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	MS (APCI) m/z (^{79}Br^{81}Br) 459.1 $(M+1)^+$
3*	3-(2-Bromo-4-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	ES/MS m/z (^{79}Br) 393 $(M+1)^+$
*Use 1.1 eq NBS and stir for 3 days.		

Example 4

3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine

[0088]



[0089] Charge an oven dried flask with 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine (0.973 g, 2.00 mmol), anhydrous dioxane (20 mL), morpholine (0.872 g, 10.0 mmol), and cesium carbonate (1.95 g, 6.00 mmol). Reflux in an oil bath (105 °C) under an inert atmosphere overnight. Confirm the reaction is complete using LC/MS. Dilute with ethyl acetate (100 mL), wash with water (50 mL), and back extract the aqueous with ethyl acetate (50 mL). Combine the organic phases, dry over magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) to 0% hexane/100% (40% dichloromethane/20% ethyl acetate/2% 7 N ammonia in methanol/38% hexane) in a step gradient of 10% increments to yield an off-white solid

(0.878 g, 89%). ES/MS m/z (^{79}Br) 491.7 $(M+1)^+$.

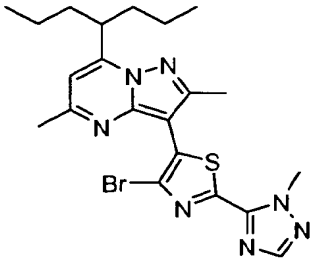
[0090] Prepare the following examples essentially as described in Example 4, using as the amine either 2.0 dimethylamine/THF or morpholine, and using THF or dioxane as the solvent. Run reactions in a sealed vessel or Schlenk tube.

Ex. No.	Chemical name	Physical data
5*	{4-Bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine	ES/MS (^{79}Br) 449.8 $(M+1)^+$.
6	3-(4-Bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	MS (APCI) m/z (^{81}Br) 466.5 $(M+1)^+$
7	{4-Bromo-S-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (^{81}Br) 424.4 $(M+1)^+$
8	{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-methyl-thiazol-2-yl}-dimethyl-amine	ES/MS m/z 358 $(M+1)^+$
9	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(4-methyl-2- morpholin-4-yl-thiazol-5-yl)-pyrazolo[1,5- *a*]pyrimidine	ES/MS m/z 400 $(M+1)^+$
*Use 6 eq of cesium carbonate.		

Example 10

3-[4-Bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propylbutyl)-pyrazolo[1,5-*a*]pyrimidine

[0091]



[0092] Charge an oven dried flask with 1-methyl-1,2,4-triazole (0.498, 6.00 mmol) and anhydrous THF (20 mL) and chill under an inert atmosphere to -78 °C. Slowly add *n*-butyl lithium (2.5 M hexane solution, 2.4 mL, 6.0 mmol) and stir 30 min. Add anhydrous zinc chloride (1.36 g, 10.0 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to warm to room temperature, stir 30 min, and add 3-(2,4-dibromothiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo [1,5-*a*] pyrimidine (0.973 g, 2.00 mmol) and dichloro[1,1'-bis(diphenylphosphino) ferrocene] palladium (II) dichloromethane (0.163 g, 0.200 mmol). Reflux the reaction overnight in an oil bath (90 °C) under an inert atmosphere. Cool the reaction to room temperature, quench with water, and dilute with ethyl acetate (100 mL). Separate and extract the aqueous portion with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (10% acetonitrile/40% THF/50% hexane) to 0% hexane/100% (10% acetonitrileM0% THF/50% hexane) in a step gradient of 10% increments to give a white solid (0.090 g, 9%). ES/MS m/z (^{79}Br) 487.7 $(M+1)^+$.

Alternate preparation:

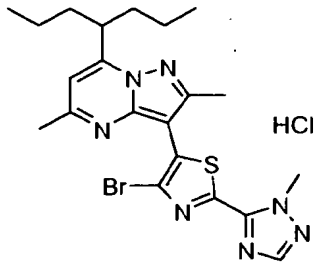
[0093] To a solution of 2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-7-(1-propyl-butyl)-pyrazolo [1,5-*a*]pyrimidine (6 g, 14.65 mmol) in acetonitrile (60 mL) add N-bromosuccinimide (2.74 g, 15.4 mmol) in one portion and stir at 22 °C for 10 h. Evaporate the solvent and dissolve the residue in a mixture of water (50 mL) and methyl-*t*-butyl ether (100 mL). Separate the organic layer and extract the aqueous layer with additional methyl-*t*-butyl ether (2 × 50 mL). Combine the organic portions and evaporate the solvent. Purify the resulting material by filtration through a silica

gel pad, eluting with hexanes/ethyl acetate (3/1). Combine the product containing fractions and evaporate the solvent. Add heptanes (25 mL) and triturate the solid. Filter the solid and dry under vacuum to afford the title compound (5.5 g, 77%). ES/MS m/z ($^{79}Br/^{81}Br$) 488/490 $(M+1)^+$.

Example 10a

3-[4-Bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propylbutyl)-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

[0094]



[0095] Dissolve 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo [1,5-*a*]pyrimidine (750 mg, 1.54 mmol) in acetone (5 mL) and add 1 M HCl in diethyl ether (1.84 mL, 1.84 mmol). Stir the mixture at room temperature for 3 h and concentrate *in vacuo.* Dissolve the residue in diethyl ether/hexane = 1/1 (5 mL) and crystallize the desired HCl salt (526 mg, 65%). ES/MS m/z (^{81}Br) 490 $(M+1)^+$; ^1H-NMR($CDCl_3$): 8.20 (s, 1H), 6.82 (s, 1H), 4.21 (s, 3H), 3.64 (m, 1H), 2.49 (m, 3H), 2.44 (s, 3H), 1.75 (m, 4H), 1.96(m, 4H), 0.81 (m, 6H).

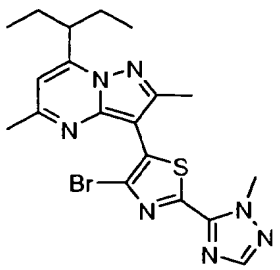
[0096] Prepare the following compound essentially as described in Example 10.

Ex. No.	Chemical name	Physical data
11*	7-(1-Ethyl-propyl)-2,5-dimethyl-3-[4-methyl-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine	ES/MS m/z 396 $(M+1)^+$
* Use 0.5 M zinc chloride in THF instead of anhydrous zinc chloride. Heat at 80 °C for 3 days.		

Example 12

3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0097]



[0098] Under nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.6 mL, 1.5 mmol) to a solution of 1-methyl-1,2,4-triazole (124.5 mg, 1.5 mmol) in THF (3 mL) at-78 °C and stir for 30 min. Add anhydrous zinc chloride (409 mg, 3.0 mmol), continue stirring for 30 min, warm up to room temperature and stir for 2 h. Add 3-(2,4-dibromothiazol-5-yl)-

7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (229 mg, 0.5 mmol), followed by tetrakis(triphenylphosine)palladium (58 mg, 0.05 mmol) and reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with saturated ammonia chloride. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes:ethyl acetate (10:2.5) to give the title compound as a yellow foam (77 mg). MS (APCI) m/z (^{79}Br) 460.4 $(M+1)^+$.

Alternate preparation from Example 21:

[0099] Add acetic acid (1 mL) and N-bromosuccinimide (4.1 g, 22 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-pyrazolo[1,5-*a*]pyrimidine (8 g, 21 mmol) in acetonitrile (80 mL). Stir the mixture 2 h at 22 °C. Then evaporate the solvent and add water (50 mL) and methyl-*t*-butyl ether (100 mL) to the resulting residue. Separate the organic portion, dry over sodium sulfate, filter, and evaporate the solvent. Recrystallize the resulting residue from isopropyl alcohol to afford the title compound (8.7 g, 90%). ES/MS (m/z): (^{79}Br/^{81}Br) 460/462 $(M+1)^+$.

Example 12a

3-(4-Bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, *p*-toluene sulfonic acid

[0100] Dissolve 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo [1,5-*a*]pyrimidine (50 mg, 0.109 mmol) in acetone (3 mL). Add a 0.25 M aqueous solution of *p*-toluene sulfonic acid (434.4 μL, 0.109 mmol) and evaporate the resulting mixture to dryness. Add ethyl acetate (12 mL) to get partial dissolution of the solids. Add methanol (1mL) to achieve a clear solution. Concentrate the solution by slow evaporation until crystals are observed. Isolate the crystals by filtration and dry under vacuum at 25 °C to obtain about 50 mg of the title compound.

[0101] Determine the stoichiometry of the salt by ion chromatography using the following HPLC conditions: column: Phenomenex Phenosphere SAX, 4.6 × 150 mm at 30 °C; mobile phase: 50% acetonitrile/50% 0.025 M sodium phosphate buffer at pH = 4.5; flow rate = 1.5 mL/min; detection: UV at 205 nm; injection volume = 5 μL; run time = 3 min. Theoretical amount calc: 27.2% tosylate; found: 28.4% tosylate (average of three HPLC runs).

Example 13

{4-Chloro-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethylamine

[0102] Charge an oven dried flask with {4-bromo-5-[2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl-dimethylamine (0.20, 0.44 mmol) and anhydrous THF (3.0 mL) and chill under an inert atmosphere to -78°C. Slowly add n-butyl lithium (1.6 M hexane solution, 0.42 mL, 0.67 mmol) and stir 30 min. Add N-chlorosuccinimide (0.120 g, 0.889 mmol) in one aliquot and stir 30 min at -78 °C. Allow the reaction to warm to room temperature, and stir for 5 h, checking the progress using LC/MS. Dilute with ethyl acetate (100 mL), wash with saturated ammonium chloride (50 mL), and back-extract the aqueous with dichloromethane (50 mL). Combine the organic phases, dry over anhydrous magnesium sulfate, filter, and concentrate under reduced pressure. Purify the resulting residue using flash chromatography, eluting with 100% hexane/0% (25% THF/hexane) to 0% hexane/100% (25% THF/hexane) in a step gradient of 10% increments to give a white solid (0.087 g, 48%). ES/MS m/z (^{35}Cl) 406.0 $(M+1)^+$.

[0103] Prepare the following examples essentially as described in Example 13 using the appropriate bromothiazole prepared above.

Ex. No.	Chemical name	Physical data
14	3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-*a*] pyrimidine	ES/MS m/z (^{35}Cl) 448.0 $(M+1)^+$
15	{4-Chloro-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidin-3-yl]-thiazol-2-yl}-dimethyl-amine	MS (APCI) m/z (^{35}Cl) 378.0 $(M+1)^+$

Preparation 18 2,4-dichlorothiazole

[0104] Cool to 5 °C a mixture of thiazolidine-2,4-dione (50 g, 0.43 mol) in phosphorus oxychloride (240 mL) and add pyridine (34 mL, 0.43 mol) over 15 min. Heat the mixture to 125 °C for 4 h and then cool to 22 °C. Remove the excess

phosphorus oxychloride by vacuum distillation and add the residue to water (1 L) chilled to a temperature of 5 °C. Extract the mixture with methylene chloride (3 × 400 mL). Combine the organic portions and evaporate the solvent to afford the title compound (50 g, 76%). EI/MS m/z : ($^{35}Cl^{35}Cl/^{35}Cl^{37}Cl^{37}Cl^{37}Cl$) 153/155/157 $(M+1)^+$.

Preparation 19

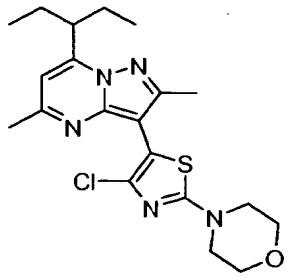
4-chloro-2-morpholino-thiazole

[0105] To a mixture of 2,4-dichlorothiazole (34 g, 0.22 mol) in acetonitrile (425 mL) add potassium carbonate (60.9 g, 0.44 mol) and then morpholine (21.2 mL, 0.225 mol) dropwise over 30 min. Reflux the mixture at 40 °C and then cool to 22 °C. Filter the mixture and evaporate the filtrate. Triturate the residue with *i*-propyl alcohol (60 mL) at 22 °C for one hour. Filter the solids and dry under vacuum to a constant weight to afford the title compound (34.5 g, 76%). ES/MS m/z (^{35}Cl) 205 $(M+1)^+$.

Example 16

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0106]



[0107] Under a nitrogen atmosphere dissolve 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (116 mg, 0.25 mmol) in THF (1.5 mL) and chill to -78 °C. Add n-butyl lithium (0.1 mL. 2.5 M in hexane, 0.25 mmol) and stir at -78 °C for 30 min. Add N-chlorosuccinimide (33.4 mg, 0.25 mmol) and stir for another 30 min, slowly warming to room temperature. After stirring overnight, quench the reaction by adding a solution of saturated ammonia chloride and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes:dichloromethane:ethyl acetate (5:5:2) to provide the title compound (54 mg). MS (APCI) m/z (^{35}Cl) 420.6 $(M+1)^+$; ^1H NMR (400 MHz, $CDCl_3$): 6.44 (s, 1H), 3.79 (t, 4H, *J*=4.8 Hz), 3.63-3.56 (m, 1H), 3.47 (t, 4H, *J*=4.8 Hz), 2.55 (s, 3H), 2.45 (s, 3H), 1.88-1.75 (m, 4H), 0.87 (t, 6H, *J*=7.5 Hz).

Alternate Preparation from Preparation 6:

[0108] Combine 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, (9 g, 26.2 mmol) and 4-chloro-2-morpholino-thiazole (7.5 g, 36.7 mmol) in dimethylformamide (90 mL) previously degassed with nitrogen. Add cesium carbonate (17.8 g, 55 mmol), copper iodide (250 mg, 1.31 mmol), triphenylphosphine (550 mg, 2.09 mmol) and palladium acetate (117 mg, 0.52 mmol). Heat the mixture to 125 °C for 16 h and then cool to 22 °C. Add water (900 mL) and extract with methyl-*t*-butyl ether (3 × 200 mL). Combine the organic portions and evaporate the solvent. Purify by silica gel chromatography eluting with hexanes/ethyl acetate (4/1) to afford the title compound (6.4 g, 62%). ES/MS m/z (^{35}Cl) 420 $(M+1)^+$.

Example 16a

3-(4-Chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine, hydrochloride

[0109] Dissolve 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.40 g, 3.33 mmol) in acetone (10 mL) at 50 °C and cool to room temperature. Add hydrogen chloride (2 M in diethyl

ether, 2.0 mL, 4.0 mmol) and stir well in a sonicator. Concentrate the solution a little and add a minimal amount of diethyl ether to crystallize the HCl salt. Cool the mixture in a refrigerator overnight. Add additional hydrogen chloride (2 M in diethyl ether, 2.0 mL, 4.0 mmol) and cool in a refrigerator. Filter the crystalline material and dry to obtain the title compound (1.15 g, 75%). ES/MS m/z (^{35}Cl) 420 $(M+1)^+$; ^{1}H NMR(CDCl3): 9.18 (br, 1H), 6.86 (s, 1H), 3.72 (m, 4H), 3.49(m, 1H), 3.39 (m, 4H), 2.48 (s, 3H), 2.38(s, 3H), 1.79 (m, 4H), 0.79 (m, 6H).

Example 17

3-(4-Bromo-2-butyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0110] Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.2 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.5 mmol) in THF (3 mL) at-78 °C. After 30 min, add 1-iodobutane (138 mg, 0.75 mmol) and continue stirring for 1 hour. Warm up to room temperature and stir for one hour. Quench the reaction by adding saturated ammonia chloride solution and extract with ethyl acetate. Dry the organic portion over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/1.5) to give the title compound as orange foam (78 mg). ES/MS m/z (^{81}Br) 437.4 $(M+1)^+$.

[0111] Prepare the following example essentially as described in Example 17.

Ex. No.	Chemical name	Physical data
18	3-(4-Bromo-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine	MS (APCI) m/z (^{81}Br) 424.6 $(M+1)^+$

Example 19

7-(1-Ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0112] Under a nitrogen atmosphere, add *n*-butyl lithium (2.5 M in hexane, 0.4 mL, 1.0 mmol) to a solution of 7-(1-ethyl-propyl)-2,5-dimethyl-3-thiazol-5-yl-pyrazolo[1,5-a]pyrimidine (300 mg, 1.0 mmol) in THF (3 mL) at -78 °C. Stir 30 min and add 1-iodomethyl methyl ether (205 mg, 1.2 mmol). Continue stirring for one hour and then slowly warm up to room temperature and stir overnight. Quench the reaction by adding saturated ammonium chloride solution and extract with ethyl acetate. Wash the organic layer with brine, dry over sodium sulfate, filter, and concentrate under vacuum to a residue. Purify the crude material by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound as a yellow foam (184 mg). MS (APCI) m/z 345.3 $(M+1)^+$.

Example 20

3-(4-Chloro-2-methoxymethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0113] Add *n*-butyl lithium (2.5 M in hexanes, 174 mL, 0.43 mmol) to a stirred solution of 7-(1-ethyl-propyl)-3-(2-methoxymethyl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine (150 mg, 0.43 mmol) in THF (3 mL) at -78 °C. Stir for 30 min and add N-chlorosuccinimide (87 mg, 0.653 mmol). Stir 30 min and then warm the reaction slowly to room temperature allowing the reaction to continue overnight. Quench the reaction by adding saturated ammonium chloride solution, extract with ethyl acetate, dry over sodium sulfate, filter, and concentrate to a residue. Purify by flash chromatography, eluting with hexanes/ethyl acetate (10/2) to give the title compound (7 mg). MS (APCI) m/z (^{35}Cl) 379.3 $(M+1)^+$.

Example 21

7-(1-Ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-pyrazolo[1,5-*a*]pyrimidine

[0114] Mix 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidine (175 mg, 0.38 mmol) and copper(I) chloride (132 mg, 1.33 mmol) in DMF (5 mL) and heat to 120 °C for 24 h. Cool to room temperature, dilute with ethyl acetate, and wash with brine. Dry the organic layer over sodium sulfate, filter, and concentrate under vacuum to a residue. Purify by flash chromatography, eluting with hexanes and then hexanes/EtOAc (10/1.8) to give a yellow-orange solid (45 mg). ES/MS m/z 382.0 $(M+1)^+$.

Alternate Preparation:

[0115] Add *n*-butyl lithium (2.5 M in hexanes, 57.6 mL, 144 mmol) to a solution of N-methyltriazole (11.95 g, 144 mmol) in THF (600 mL) at -78 °C under a nitrogen atmosphere, keeping the temperature below -74 °C during the addition. Then add zinc chloride, dry powder, (26 g, 192 mmol) in one portion and warm the mixture to 22 °C in one hour. Add 7-(1-ethyl-propyl)-3-(2-iodo-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (12.5 g, 29 mmol) and tetrakis(triphenyl) phosphine palladium catalyst (1.15 g, 0.01 mol) in one portion and heat the mixture to reflux under nitrogen for 8 h. Cool the mixture to 22 °C and add water (300 mL). Separate the organic layer and extract the aqueous layer with methyl-*t*-butyl ether (2 × 200 mL). Combine the organic portions, dry over sodium sulfate, filter, and evaporate the solvent. Purify by passing over a silica gel pad eluting with hexanes/ethyl acetate (4/1) to afford the title compound (8 g, 72%). ES/MS m/z 382 $(M+1)^+$.

Example 22

3-(4-Chloro-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0116] Stir a mixture of 7-(1-ethyl-propyl)-2,5-dimethyl-3-[2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-pyrazolo [1,5-*a*]pyrimidine (20 mg, 0.052 mmol) and N-chlorosuccinimide (7.6 mg, 0.0569 mmol) in dichloromethane (0.5 mL) and acetonitrile (0.5 mL) at room temperature overnight in a vial. Concentrate to a residue. Purify by flash chromatography, eluting with hexanes and then with hexanes/ethyl acetate (10/1.5) to give the title compound (16 mg). ES/MS m/z (^{35}Cl) 416.0 $(M+1)^+$.

Example 23

7-(1-Ethyl-propyl)-3-(4-methoxy-2-morpholin-4-yl-thiazol-5-yl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0117] Stir a mixture of 3-(4-bromo-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (162 mg, 0.35 mmol), sodium methoxide (57 mg, 1.05 mmol) and copper(I) iodide (67 mg, 0.35 mmol) in methanol (3 mL) in a sealed 4-mL vial for 15 h at 120 °C. Cool to room temperature, remove the solid by filtration, and concentrate the filtrate under vacuum. Purify the residue by flash chromatography, eluting with hexanes/THF (10/2). Recrystallize the material from methanol to give the title compound (20 mg). ES/MS m/z 416.0 $(M+1)^+$.

Preparation 20

4-Bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde

[0118] Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexanes, 0.312 mL, 0.50 mmol) to a THF solution (2.5 mL) of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (230 mg, 0.50 mmol) at -78 °C and stir for 30 min. Add a THF (0.5 mL) solution of N-formyl morpholine (58 mg, 0.50 mmol). Stir for one hour, then store the reaction at -20 °C overnight. Warm the reaction to room temperature, dilute with ether, and quench by adding 4 N HCl (4 mL). Separate and extract the organic phase with 4 N HCl (2 × 4 mL). Combine the aqueous portions, treat with solid sodium bicarbonate to pH = 8 to 9 and then extract with diethyl ether. Combine all the organic layers, wash with brine, dry over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with hexanes/dichloromethane/ethyl acetate (5/5/1) to give the title compound (154 mg). MS (APCI) m/z (^{81}Br) 409.0 $(M+1)^+$.

Example 24

3-(4-Bromo-2-morpholin-4-yl-methyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0119] Combine 4-bromo-5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-thiazole-2-carbaldehyde (150 mg, 0.368 mmol), morpholine (35 mg, 0.405 mmol) and sodium triacetoxyborohydride (97 mg, 0.46 mmol), in dichloromethane (3 mL) and methanol (0.5 mL). Stir overnight, add additional morpholine (35 mg, 0.405 mmol), and sodium triacetoxyborohydride (97 mg, 0.46 mmol), and stir 4 h more. Remove the solvent under vacuum, dilute with dichloromethane, and wash with brine. Dry the organic phase over sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material using flash chromatography, eluting with dichloromethane:2 M ammonia in methanol (10:1) to give a mixture. Purify the mixture using a reverse phase column, eluting with water/acetonitrile (80/20) to water/acetonitrile (10/90) to give the title compound (20 mg). ES/MS m/z (^{81}Br) 480.0 $(M+1)^+$.

Example 25

3-(4-Bromo-2-pyridin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine

[0120] Under a nitrogen atmosphere, add *n*-butyl lithium (1.6 M in hexane, 0.312 mL, 0.5 mmol) to a solution of 3-(2,4-dibromo-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (229 mg, 0.5 mmol) in THF (4 mL) at -78 °C. After stirring for 30 min, add anhydrous zinc chloride (264 mg, 1.5 mmol) and continue stirring for 30 min. Warm the reaction to room temperature and stir for one hour. Add 4-iodopyridine (103 mg, 0.5 mmol), followed by 1,1'-bis (diphenylphosphino)ferrocene palladium (II) chloride (dichloromethane adduct) (0.40.8 mg, 0.05 mmol). Heat the reaction to reflux overnight. Cool to room temperature, dilute with ethyl acetate, and wash with water and brine. Dry the organic layer over sodium sulfate, filter, and concentrate to a residue. Purify the crude material by flash chromatography, eluting with dichloromethane:2 N ammonia in methanol (10:0.75) to give a mixture. Purify the mixture using a reverse phase column, eluting with water:acetonitrile = 80:20 to water: acetonitrile = 10:90, to give the title compound (19 mg). ES/MS m/z (^{79}Br) 456.0 $(M+1)^+$.

Preparation 21

4-Trifluoromethyl-thiazole-2-ylamine

[0121] Add thiourea (4.0 g, 52.3 mmol) and 3-bromo-1,1,1-trifluoropropan-2-one (5.5 mL, 10 g, 52.3 mmol) to ethanol (100 mL) and heat at 50 °C for 2 h. Cool to room temperature and concentrate to dryness. Dissolve the residue in water and adjust the pH to >12 with 2 M NaOH. Extract with diethyl ether (4×). Dry the combined organic extracts with sodium sulfate, filter, and concentrate under vacuum. Purify the resulting material by silica gel chromatography (CH_2Cl_2) to obtain the title compound (6.9 g, 79%). ES/MS m/z 169 $(M+1)^+$.

Preparation 22

5-Bromo-4-trifluoromethyl-thiazol-2-ylamine, hydrobromide

[0122] Add bromine (2.0 mL, 6.28 g, 39.3 mmol) dropwise to an ice-bath cooled solution of 4-trifluoromethyl-thiazole-2-ylamine (6.0 g, 35.7 mmol) in diethyl ether (60 mL). Stir for one hour after the addition is complete and then warm to room temperature. Collect the solids by filtration and wash with diethyl ether to obtain the title compound (10.5 g, 90%). ES/MS m/z (^{79}Br/^{81}Br) 247/249 $(M+1)^+$.

Preparation 23

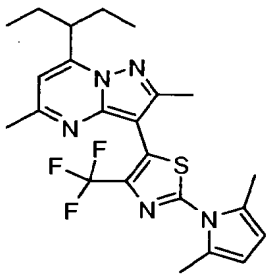
5-Bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole

[0123] Add hexane-2,5-dione (3.5 mL, 3.4 g, 30.2 mmol) to a solution of 5-bromo-4-trifluoromethyl-thiazol-2-ylamine hydrobromide (9.0 g, 27.4 mmol) in methanol (60 mL). Stir at room temperature overnight. Add phosphate buffer (50 mL, pH = 7). Collect the resulting precipitate by filtration, washing with water. Dissolve the filter cake in CH_2Cl_2 and dry over sodium sulfate. Filter and concentrate under vacuum to obtain the title compound (8.2 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 2H), 2.27 (s, 6H).

Example 26

3-[2-(2,5-Dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0124]



[0125] Cool a solution of 5-bromo-2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazole (2.2 g, 6.6 mmol) in THF (25 mL) in a dry ice bath. Add *t*-butyl lithium (1.7 M in pentane, 8.5 mL, 14.5 mmol) dropwise. Stir for 45 min and then add zinc chloride (0.5 M in THF, 14.6 mL, 7.3 mmol) dropwise. Stir 5 min and remove the cooling bath. Stir 30 min and then add 7-(1-ethyl-propyl)-3-iodo-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.5 g, 4.4 mmol) and bis(tri-*t*-butylphosphine)palladium (0) (450 mg, 0.9 mmol). Reflux for 24 h. Cool the reaction, pour the mixture into diethyl ether, and wash with water (2×). Extract the combined water layers with diethyl ether. Dry the combined organic portions over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (75-100% CH_2Cl_2 in hexanes) to give the title compound (1.47 g, 72%). HR-ToF-MS m/z calcd for $C_{23}H_{26}F_3N_5S+H^+$: 462.1939, found: 462.1915.

Example 27

5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine

[0126] Add hydroxylamine (2 mL, 50% in water) to a solution of 3-[2-(2,5-dimethyl-pyrrol-l-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (1.1 g, 2.3 mmol) in acetic acid (10 mL). Heat the reaction to 80 °C for 6 h. Cool to room temperature. Pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography (40% ethyl acetate in hexanes) to give the title compound (0.76 g, 87%). ES/MS m/z 384 $(M+1)^+$.

Preparation 24

3-(2-Bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine

[0127] Heat a mixture of copper(II) bromide (540 mg, 2.4 mmol) and *t*-butylnitrite (0.36 mL, 310 mg, 3.0 mmol) in acetonitrile (20 mL) to 60 °C. Add 5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamine (755 mg, 2.0 mmol) as a solid. Heat the reaction to 80 °C for 2 h. Cool the reaction, pour into diethyl ether and extract with water (3×). Dry the organic layer over sodium sulfate, filter, and concentrate to dryness under vacuum. Purify the resulting residue by silica gel chromatography in CH_2Cl_2 to give the title compound (0.77 g, 87%). ES/MS m/z ($^{79}Br/^{81}Br$) 447, 449 $(M+1)^+$.

Example 28

{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-dimethyl-amine

[0128] Heat a sealed tube containing 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (313 mg, 0.7 mmol), and dimethyl amine (2 M in THF, 4 mL, 8 mmol) in methanol (4 mL) to 80 °C for 2 h. Cool the reaction and concentrate under vacuum. Purify the resulting residue by silica gel chromatography, eluting with 0-30% ethyl acetate in CH_2Cl_2, to give the title compound (0.28 g, 97%). HR-ToF-MS m/z calcd for $C_{19}H_{24}F_3N_5S+H^+$ 412.1770, found: 412.1783.

[0129] Prepare the following example essentially as described for Example 28 with the exception that the reaction is refluxed for 8 h.

Ex. No.	Chemical name	Physical data
29	7-(1-Ethyl-propyl)-2,5-dimethyl-3-(2-morpholin-4-yl-4-trifluoromethyl-thiazol-5-yl)-pyrazolo[1,5-*a*] pyrimidine	HR-ToF-MS m/z calcd for $C_{21}H_{26}F_3N_5OS+H^+$: 454.1873, found: 454.1873, found: 454.1888

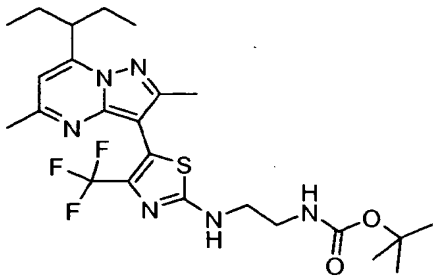
Example 30

N-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-acetamide

[0130] Add hydroxylamine (50% in water, 5 mL,) to a solution of 3-[2-(2,5-dimethyl-pyrrol-1-yl)-4-trifluoromethyl-thiazol-5-yl]-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (2.4 g, 5.2 mmol) in acetic acid (25 mL). Heat the reaction to 80 °C for 72 h. Cool the reaction to room temperature, pour into diethyl ether and wash with 2 M NaOH (2×) and then once with water. Dry the organic portion over sodium sulfate, filter, and concentrate to dryness. Purify the resulting residue by column chromatography, eluting with 40% ethyl acetate in hexanes to give the title compound (0.28 g, 13%). HR-ToF-MS m/z calcd for $C_{19}H_{22}F_3N_5OS+H^+$ 426.1575, found: 426.1565.

Example 31

[0131] (2- {5-[7-(1- Ethyl- propyl)- 2,5- dimethyl- pyrazolo [1,5-*a*] pyrimidin- 3- yl]- 4- trifluoromethyl- thiazol- 2- ylamino}-ethyl)-carbamic acid *tert*-butyl ester



[0132] Add (2-amino-ethyl)-carbamic acid *tert*-butyl ester (0.5 mL, 506 mg, 3.2 mmol) to a solution of 3-(2-bromo-4-trifluoromethyl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine (100 mg, 0.22 mmol) and triethylamine (0.3 mL, 222 mg, 2.2 mmol) in methanol (1 mL). Evaporate off the methanol and heat to 80 °C overnight. Cool the reaction to room temperature and concentrate under vacuum. Purify the resulting residue by column chromatography, eluting with 10-50% ethyl acetate in CH_2Cl_2, to give the title compound (0.11 g, 97%). ES/MS m/z 527.2 $(M+1)^+$.

[0133] Prepare the compounds below as essentially described in Example 31 using the appropriate amine.

Prep. or Ex. No.	Chemical name	Physical data
Prep. 25*	[2-({5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-propyl-amino)-ethyl]-carbamic acid tert-butyl ester	ES/MS m/z 569.3 $(M+1)^+$
Prep. 26**	(S)-(1-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester	ES/MS m/z 553.3 $(M+1)^+$
Ex. 32***	*N*-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-*N*,*N*'-dipropyl-ethane-1,2-diamine, hydrochloride	ES/MS m/z 511.2 $(M+1)^+$
* Heat at reflux in EtOH overnight. Evaporate EtOH and heat at 110 °C for 24 h. ** Heat at 80 °C in EtOH overnight. *** Make the HCl salt and recrystallize from EtOAc/hexanes.		

Example 33

N^1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-ethane-1,2-diamine, hydrochloride

[0134] Add (2-{5-[7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-ylamino}-ethyl)-carbamic acid *tert*-butyl ester (101 mg, 0.192 mmol) to 1 M HCl in methanol (1 mL). Heat the reaction at 70 °C overnight. Cool the reaction and concentrate under vacuum from methanol/ethyl acetate. Triturate the resulting residue with ethyl acetate to obtain the title compound (64 mg, 78%). ES/MS m/z 427.0 $(M+1)^+$.

[0135] Prepare the following examples essentially as described for Example 33.

Ex. No.	Chemical name	Physical data
34	N^1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-N^1-propyl-ethane-1,2-diamine, hydrochloride	ES/MS m/z 469.2 $(M+1)^+$
35	(*S*)-1-{5-[7-(1-Ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidin-3-yl]-4-trifluoromethyl-thiazol-2-yl}-pyrrolidin-3-ylamine, hydrochloride	ES/MS m/z 453.0 $(M+1)^+$

Example A

In Vivo Potency Assessment Using Ex Vivo Binding

[0136] To assess in vivo potency, a compound of the present invention is evaluated using ex vivo binding. Using the procedures as provided in D. R. Gehlert et al., EJP 509: 145-153 (2005), a compound is administered to a rat via the oral route. The binding of ^{125}I-sauvagine to the cerebellum is then assessed ex vivo as described in Gehlert *et al.* For example, Example 15 provides 65% inhibition at 10 mg/kg.

Example B

CRF1 Filter Binding Assay

[0137] The limitations of plasmid-based human CRF 1 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF1 cell line is used to prepare membranes and binding reactions (200 μL) are set up as follows: 50 μL of ^{125}I-sauvagine (0.2 nM final), 50 μL compound and 100 μL CRF1 membrane (25 μg/reaction). The reactions are incubated at room temperature for 2 h and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Triplicate determinations are typically run and the median data points plotted by Graph Pad Prism.

[0138] Using this assay, the exemplified compounds of the present invention inhibit the binding of ^{125}I-Sauvagine (4 nM) in roller/adherent cells with a Ki (inhibition constant) below 1 μM. For example, Example 15 exhibits a Ki of 6.2 nM.

Example C

CRF2 Filter Binding Assay

[0139] The limitations of plasmid-based human CRF2 expression, in terms of generating a recombinant cell line with sufficient receptor density to develop a binding assay, are overcome by using a Phoenix retroviral expression system licensed from Stanford. The stable HEK-hCRF2 cell line is used to prepare membranes and binding reactions (200 μL) are set up as follows: 50 μL of ^{125}I-sauvagine (0.2 nM final concentration), 50 μL compound and 100 μL CRF2 membrane (25 μg/reaction). The reactions are incubated at room temperature for 2 hours and then terminated by filtration through pre-treated FB Millipore glass fiber filter plates (96 well). The plates are washed twice with ice-cold assay buffer (50 mM tris, 12.5 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, 0.05% BSA, pH 7.2), air dried over night and counted with 100 μL Microscint 40 in a MicroBeta counter. Non-specific binding (NSB) is determined in the presence of 0.5 μM non-labeled sauvagine. Alternatively, compounds are evaluated using a Scintillation Proximity assay. This assay is set up as follows: 50 μL of ^{125}I-Sauvagine (0.2 nM final concentration), 50 μL compound or non-labelled sauvagine (NSB) and 100 μL

containing 250 μg wheat germ agglutinin (WGA) SPA beads and CRF2 membrane (1.5 μg/reaction). Plates are incubated for 4-5 h at room temperature and then centrifuged at 200 X g for 10 min. Bound radioactivity is assessed using a Wallac Trilux scintillation counter. Binding is assessed typically using triplicate determinations and the median data points plotted by Graph Pad Prism. Compounds are initially screened at a fixed concentration and, if sufficient activity is noted, subsequent concentration-response curves are generated.

[0140] Particular exemplified compounds of the present invention are tested in the CRF2 binding assay and exhibit weak affinity for the CRF2 receptor. For example, Example 15 exhibits 11% inhibition at a concentration of 50 μM. This result suggests that the compounds of the present invention are selective for the CRF 1 receptor, (relative to CRF2).

Example D

Bioavailability and Pharmacokinetic Properties

[0141] The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. The volume of distribution refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: Vdist = amount of drug in the body/ concentration of drug in blood or plasma (Goodman and Gillman's). For a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, Vdist can be used to determine a loading dose to achieve a steady state concentration.

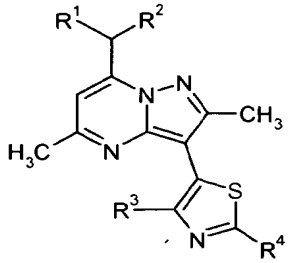
[0142] To test for volume of distribution, Male Sprague Dawley rats (N=3) are administered a single 1 mg/kg intravenous dose of compound. Multiple plasma samples are collected at time points from 0.08 to 24 hours post-dose. The plasma samples are analyzed by LC/MS/MS to determine the plasma concentrations. Plasma pharmacokinetic calculations are performed to determine the pharmacokinetic parameters including Vdist and plasma clearance (Clp).

[0143] Compounds of the present invention preferably have favorable bioavailability profiles. For example, a majority of commercial CNS and cardiovascular drugs exhibit a human Vdist of <10 L/Kg. In comparison with CRF antagonists, CP154526 (Schulz et al., Proc. Natl. Acad. Sci. (USA), 93:10477 (1996)) and NBI30775 (Chen et al., Drug Development Research, 65:216 (2005)), which exhibit a rat Vdist of 114 L/Kg and 76 L/Kg, respectively, when analyzed separately. Example 15 of the present invention, when analyzed separately, exhibits a rat Vdist of only 7.2 L/Kg following a single intravenous dose of 1 mg/kg.

[0144] Further, the plasma clearance (CLp) is a measure of the rate of removal of the drug from the body. Following an intravenous dose and first-order kinetics, the plasma clearance may be determined using the following equation: CLp = Dose/ AUC, where AUC is the total area under the curve that describes the concentration of the drug in the plasma as a function of time from zero to infinity. Reference CRF antagonists CP154526 and NBI37582 exhibit rat clearance (CLp) of 83 and 306 mL/min/kg, respectively, when analyzed separately, following a single intravenous dose, while Example 15 of the present invention, when analyzed separately, exhibits a rat CLp of only 23.6 mL/min/kg.

Claims

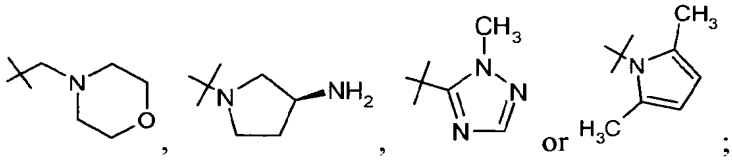
1. A compound of Formula I



Formula I

wherein:

R^1 and R^2 are independently ethyl or *n*-propel;
R^3 is hydrogen, Cl, Br, methyl, trifluoromethyl or methoxy;
R^4 is hydrogen, Br, R^aR^bN-, methoxymethyl, *n*-butyl, acetamido, pyridin-4-yl, morpholin-4-yl,

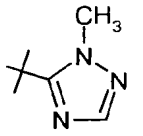


R^a and R^b are independently hydrogen, C_1-C_3alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$-, or $CH_3CH_2CH_2NHCH_2CH_2$-; or a pharmaceutically acceptable salt thereof.

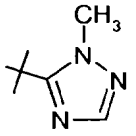
2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl, Br, methyl or trifluoromethyl.

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^3 is Cl or Br.

4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^aR^bN-, pyridin-4-yl, morpholin-4-yl, or



5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is morpholin-4-yl or



6. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is R^aR^b- and R^a and R^b are independently C_1-C_3alkyl.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-[4-bromo-2-(2-methyl-2*H*-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)- pyrazolo[1,5-*a*]pyrimidine.

8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-(4-bromo-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethylpropyl)-2,5-dimethyl-pyrazolo[1,5-*a*]pyrimidine.

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidine.

10. A pharmaceutical composition comprising: a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

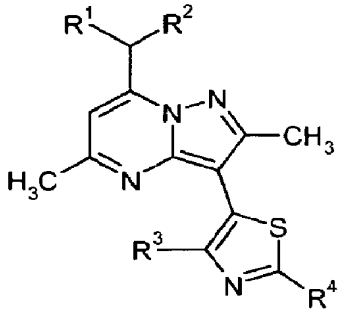
11. A compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in therapy.

12. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of anxiety or depression.

13. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of alcohol or substance abuse.

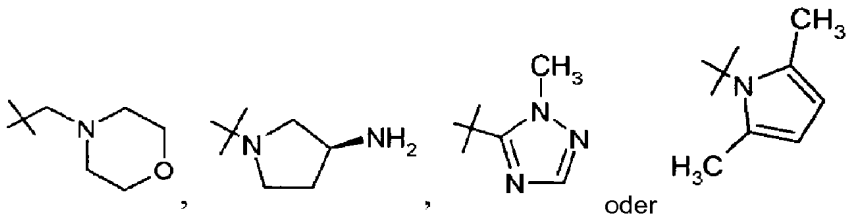
Patentansprüche

1. Verbindung der Formel I



Formel I

worin
R^1 und R^2 unabhängig voneinander für Ethyl oder n-Propyl stehen;
R^3 für Wasserstoff, Cl, Br, Methyl, Trifluormethyl oder Methoxy steht;
R^4 für Wasserstoff, Br, R^aR^bN-, Methoxymethyl, n-Butyl, Acteamido, Pyridin-4-yl, Morpholin-4-yl,

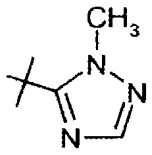


steht;
R^a und R^b unabhängig für Wasserstoff, C_1-C_3Alkyl, $H_2NCH_2CH_2$-, $(CH_3)_3COC(O)NHCH_2CH_2$- oder $CH_3CH_2CH_2NHCH_2CH_2$- stehen;
oder ein pharmazeutisch akzeptables Salz hiervon.

2. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^3 für Cl, Br, Methyl oder Trifluormethyl steht.

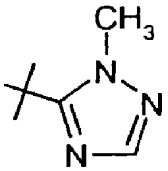
3. Verbindung nach Anspruch 1 oder 2 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^3 für Cl oder Br steht.

4. Verbindung nach einem der Ansprüche 1 bis 3 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für R^aR^bN-, Pyridin-4-yl, Morpholin-4-yl oder



steht.

5. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für Morpholin-4-yl oder



steht.

6. Verbindung nach einem der Ansprüche 1 bis 4 oder ein pharmazeutisch akzeptables Salz hiervon, worin R^4 für R^aR^bN- steht und R^a und R^b unabhängig für C_1-C_3Alkyl stehen.

7. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-[4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-dimethyl-7-(1-propyl-butyl)-pyrazolo[1,5-α]pyrimidin.

8. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Brom-2-(2-methyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-α]pyrimidin.

9. Verbindung nach Anspruch 1 oder ein pharmazeutisch akzeptables Salz hiervon, nämlich 3-(4-Chlor-2-morpholin-4-yl-thiazol-5-yl)-7-(1-ethyl-propyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin.

10. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon und einen pharmazeutisch akzeptablen Hilfsstoff umfasst.

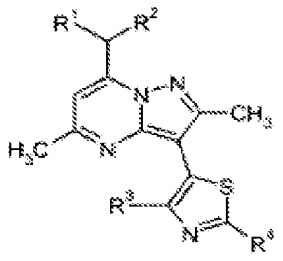
11. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung in der Therapie.

12. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Angst oder Depression.

13. Verbindung nach einem der Ansprüche 1 bis 9 oder ein pharmazeutisch akzeptables Salz hiervon zur Verwendung bei der Behandlung von Alkohol- oder Substanzmissbrauch.

Revendications

1. Composé répondant à la formule I

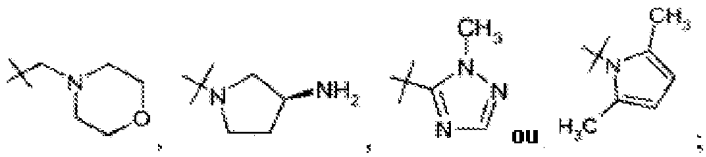


Formule I

dans laquelle :

R^1 et R^2 représentent, de manière indépendante, un groupe éthyle ou un groupe *n*-propyle ;
R^3 représente un atome d'hydrogène, un atome de chlore, un atome de brome, un groupe méthyle, un groupe trifluorométhyle ou un groupe méthoxy ;
R^4 représente un atome d'hydrogène, un atome de brome, un groupe R^aR^bN-, un groupe méthoxyméthyle, un groupe *n*-butyle, un groupe acétamido,

un groupe pyridin-4-yle, un groupe morpholin-4-yle,

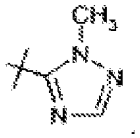


R^a et R^b représentent, de manière indépendante, un atome d'hydrogène, un groupe alkyle en C_1-C_3, un groupe $H_2NCH_2CH_2$-, un groupe $(CH_3)_3COC(O)NHCH_2CH_2$-, ou un groupe $CH_3CH_2CH_2NHCH_2CH_2$-;
ou un de ses sels pharmaceutiquement acceptables.

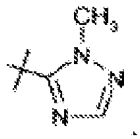
2. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^3 représente un atome de chlore, un atome de brome, un groupe méthyle ou un groupe trifluorométhyle.

3. Composé selon la revendication 1 ou 2, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^3 représente un atome de chlore ou un atome de brome.

4. Composé selon l'une quelconque des revendications 1 à 3, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe R^aR^bN-, un groupe pyridin-4-yle, un groupe morpholin-4-yle ou un groupe



5. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe morpholin-4-yle ou un groupe



6. Composé selon l'une quelconque des revendications 1 à 4, ou un de ses sels pharmaceutiquement acceptables, dans lequel R^4 représente un groupe R^aR^bN- et R^a et R^b représentent, de manière indépendante, un groupe alkyle en C_1-C_3.

7. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-[4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl]-2,5-d iméthyl-7-(1-propyl-butyl)-pyrazolo[1,5-a]-pyrimidine.

8. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-bromo-2-(2-méthyl-2H-[1,2,4]triazol-3-yl)-thiazol-5-yl)-7-(1-éthylpropyl)-2,5-diméthyl-pyrazolo[1,5-a]-pyrimidine.

9. Composé selon la revendication 1, ou un de ses sels pharmaceutiquement acceptables, qui est la 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-7-(1-éthyl-propyl)-2,5-diméthyl-pyrazolo[1,5-a]pyrimidine.

10. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, et un excipient pharmaceutiquement acceptable.

11. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser en thérapie.

12. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'anxiété ou de la dépression.

13. Composé selon l'une quelconque des revendications 1 à 9, ou un de ses sels pharmaceutiquement acceptables, à utiliser dans le traitement de l'abus d'alcool ou d'autres drogues.

REFERENCES CITED IN THE DESCRIPTION

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 March 2005 (10.03.2005)

PCT

(10) International Publication Number
WO 2005/020910 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/027600

(22) International Filing Date: 26 August 2004 (26.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/498,148 27 August 2003 (27.08.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

(57) **Abstract:** The present invention provides compositions and methods for the treatment of ischemic mediated central nervous system disorder or injury. More particularly, the invention provides a combination therapy for the treatment of a central nervous system ischemic mediated disorder or injury comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

WO 2005/020910 A2

COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

FIELD OF THE INVENTION

[0001] The present invention provides compositions and methods for the treatment of reduced blood flow to the central nervous system. More particularly, the invention is directed toward a combination therapy for the treatment or prevention of ischemic-mediated central nervous system disorders or injury, including ischemic stroke, comprising the administration to a subject of a cyclooxygenase-2 selective inhibitor in combination with a corticotropin releasing factor antagonist.

BACKGROUND OF THE INVENTION

[0002] The continued increase in the incidence of ischemic-mediated central nervous system damage, including ischemic stroke, provides compelling evidence that there is a continuing need for better treatment strategies. Stroke, for example, is consistently the second or the third leading cause of death annually and the leading producer of disability among adults in the United States and western countries. Moreover, roughly 10% of patients with stroke become heavily handicapped, often needing attendant care.

[0003] The pathology underlying ischemic-mediated central nervous system injury has been elucidated. Generally speaking, the normal amount of perfusion to brain gray matter is 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs only when the flow of blood falls below a certain level (approximately 8-10 mL/100 g of brain tissue/min), while at slightly higher levels the tissue remains alive but not able to function. For example, most strokes culminate in a core area of cell death (infarction) in which blood flow is so drastically reduced that the cells usually cannot recover. This threshold seems to occur when cerebral blood flow is 20 percent of normal or less. Without neuroprotective agents, nerve cells facing 80 to 100 percent ischemia will be irreversibly damaged within a few minutes. Surrounding the ischemic core is another area of tissue called the "ischemic penumbra" or "transitional zone" in which cerebral blood flow is between 20 and 50 percent of normal. Cells in this area are endangered, but not yet irreversibly damaged. Thus in the acute stroke, the affected central core brain tissue may die while the more peripheral tissues

remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives.

[0004] At the cellular level, if left untreated, brain or spinal cell injury and death progress in a stepwise manner rapidly within the core infarction, and over time within the ischemic penumbra. Without adequate blood supply, brain or spinal cells lose their ability to produce energy, particularly adenosine triphosphate (ATP). When this energy failure occurs, brain or spinal cells become damaged and will die if critical thresholds are reached. Immediate cell death within the ischemic core is typically necrotic, while cell death in the penumbra may be either necrotic or apoptotic. It is believed that there are an immense number of mechanisms at work causing brain or spinal cell damage and death following energy failure. Each of these mechanisms represents a potential route for intervention. One of the ways brain cells respond to energy failure is by elevating the concentration of intracellular calcium. Worsening this and driving the concentrations to dangerous levels is the process of excitotoxicity, in which brain cells release excessive amounts of glutamate, a neurotransmitter. This stimulates chemical and electrical activities in receptors on other brain cells, which leads to the degradation and destruction of vital cellular structures. Brain cells ultimately die as a result of the actions of calcium-activated proteases (enzymes which digest cell proteins), lipases (enzymes which digest cell membranes) and free radicals formed as a result of the ischemic cascade.

[0005] No drug therapy has yet been proven completely effective in preventing brain damage from cerebral ischemia. Interventions have been directed toward salvaging the ischemic penumbra and reducing its size. Restoration of blood flow is the first step toward rescuing the tissue within the penumbra. Therefore, timely recanalization of an occluded vessel to restore perfusion in both the penumbra and in the ischemic core is one treatment option employed. Partial recanalization also markedly reduces the size of the penumbra as well. Moreover, intravenous tissue plasminogen activator and other thrombolytic agents have been shown to have clinical benefit if they are administered within a few hours of symptom onset. Beyond this narrow time window, however, the likelihood of beneficial effects is reduced and hemorrhagic complications related to thrombolytic agents become excessive, seriously compromising their therapeutic value. Hypothermia decreases the size of the ischemic insult in both anecdotal clinical and laboratory reports. In addition, a wide variety of agents have been shown to reduce infarct volume in animal models. These agents

include pharmacologic interventions that involve thrombolysis, calcium channel blockade, and cell membrane receptor antagonism have been studied and have been found to be beneficial in animal cortical stroke models. But there is a continuing need for improved treatment regimens following ischemic-mediated central nervous system injury.

[0006] Corticotropin releasing factor ("CRF"), also referred to as corticotropin releasing hormone ("CRH"), is a 41 amino acid neuropeptide hormone. This peptide is the major physiologic regulator of the basal and stress-induced production and release of adrenocorticotropic hormone ("ATCH"), β-endorphin, and other peptides from the pituitary via binding of CRF to its several receptors. ACTH release leads to the release of cortisol and other adrenal steroids. Important functions affected by the action of CRF include behavior, temperature regulation, food intake, reproduction, memory and learning, and can also induce seizures (Wong et al., *NeuroReport*, 6:13 (1995) 1785-1788 Increasing evidence exists to implicate the involvement of CRF in the pathogenesis of ischemic brain damage (Mackay et al., J. Cerebral Blood Flow and Metabolism (2001) 21:1208-1214; and DeVries et al. *Proc. Nat'l. Academy Science*, (2001) 98:11824-11828). CRF has also been implicated as being neurotoxic, being involved in neurodegeneration following cerebral ischemia (Lyons et al., *Brain Research*, 545 (1991) 339-342); Wong et al. (1995)). Additionally, several authors have noted that in humans, post-stroke concentrations of cortisol are predictive of stoke outcome, high cortisol concentrations being associated with increased morbidity and mortality (Feibel et al., *JAMA* (1977) 238: 1374-1376; Olsson, t., *J. Int. Med.* (1990) 228: 177-181).

[0007] Several recent studies have found that the administration of a corticotropin releasing factor antagonist reduces the extent of stroke-induced brain damage when administered to a subject shortly before or after the onset of the ischemic cascade. In one study, it was shown that a low dose of the corticotropin releasing factor antagonist α-helical CRF 9-41 in combination with a vehicle administered via injection either 30 minutes before or 10 minutes after a unilateral, permanent middle cerebral artery occlusion (MCAo) could markedly inhibit (by over 60%) the volume of the infarction (Strijbos, et al., *Brain Research*, 656 (1994) pp. 405-408). Corticotropin releasing factor antagonists, and in particular α-helical CRF, have also been found to demonstrate a neuroprotective effect in a dose-dependent manner (Lyons et al. (1991)). In addition, it appears that corticotropin releasing factor antagonists demonstrate an

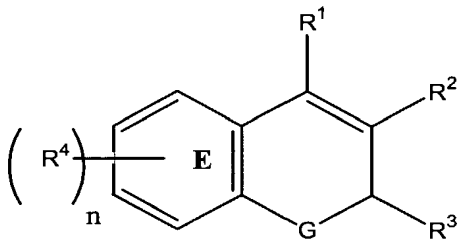
ability to inhibit neuronal damage induced by pharmacological activation of NMDA receptors , particularly in the striatum, indicating that NMDA receptor-mediated neurotoxicity is at least in part due to the release of endogenous corticotropin releasing factor (Strijbos et al. (1994)).

[0008] Moreover, several studies indicate that cyclooxygenase-2 is involved in the inflammatory component of the ischemic cascade. Cyclooxygenase-2 expression is known to be induced in the central nervous system following ischemic injury. In one study, it was shown that treatment with a cyclooxygenase-2 selective inhibitor reduced infarct volume in mice subjected to ischemic brain injury (Nagayama et al., (1999) J. Cereb. Blood Flow Metab.19(11):1213-19). A similar study showed that cyclooxygenase-2 deficient mice have a significant reduction in brain injury produced by occlusion of the middle cerebral artery when compared to mice that express cyclooxygenase-2 (Iadecola et al., (2001) PNAS 98:1294-1299). Another study demonstrated that treatment with cyclooxygenase-2 selective inhibitor results in improved behavioral deficits induced by reversible spinal ischemia in rabbits (Lapchak et al., (2001) Stroke 32(5):1220-1230).

SUMMARY OF THE INVENTION

[0009] Among the several aspects of the invention is provided a method for the treatment of ischemic mediated central nervous system disorders in a subject. The method comprises administering to the subject a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof in combination with a corticotropin releasing factor antagonist or a pharmaceutically acceptable salt or a prodrug thereof.

[0010] In one embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof is a member of the chromene class of compounds. For example, the chromene compound may be a compound of the formula



(I)

[0011] wherein:

[0012] n is an integer which is 0, 1, 2, 3 or 4;

[0013] G is O, S or NR^a;

[0014] R^a is alkyl;

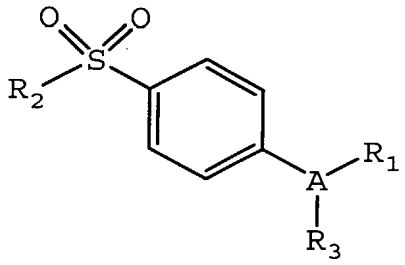
[0015] R^1 is H or aryl;

[0016] R^2 is carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl or alkoxycarbonyl;

[0017] R^3 is haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro or alkylsulfonyl; and

[0018] each R^4 is independently H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, or alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0019] In another embodiment, the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or a prodrug thereof comprises a compound of the formula



[0020] wherein:

[0021] A is a partially unsaturated or unsaturated heterocyclyl ring or a partially unsaturated or unsaturated carbocyclic ring;

[0022] R_1 is heterocyclyl, cycloalkyl, cycloalkenyl or aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0023] R^2 is methyl or amino; and

[0024] R^3 is H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, or N-alkyl-N-arylaminosulfonyl.

[0025] In yet another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919.

[0026] Other aspects of the invention are described in more detail below.

ABBREVIATIONS AND DEFINITIONS

[0027] The term "acyl" is a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and trifluoroacetyl.

[0028] The term "alkenyl" is a linear or branched radical having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl" also are radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0029] The terms "alkoxy" and "alkyloxy" are linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

[0030] The term "alkoxyalkyl" is an alkyl radical having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

[0031] The term "alkoxycarbonyl" is a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl porions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

[0032] Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" is a linear, cyclic or branched radical having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

[0033] The term "alkylamino" is an amino group that has been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

[0034] The term "alkylaminoalkyl" is a radical having one or more alkyl radicals attached to an aminoalkyl radical.

[0035] The term "alkylaminocarbonyl" is an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above.

[0036] The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl

radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

[0037] The term "alkylthio" is a radical containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

[0038] The term "alkylthioalkyl" is a radical containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

[0039] The term "alkylsulfinyl" is a radical containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

[0040] The term "alkynyl" is a linear or branched radical having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0041] The term "aminoalkyl" is an alkyl radical substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like.

[0042] The term "aminocarbonyl" is an amide group of the formula -C(=O)NH2.

[0043] The term "aralkoxy" is an aralkyl radical attached through an oxygen atom to other radicals.

[0044] The term "aralkoxyalkyl" is an aralkoxy radical attached through an oxygen atom to an alkyl radical.

[0045] The term "aralkyl" is an aryl-substituted alkyl radical such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl

may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

[0046] The term "aralkylamino" is an aralkyl radical attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" are amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

[0047] The term "aralkylthio" is an aralkyl radical attached to a sulfur atom.

[0048] The term "aralkylthioalkyl" is an aralkylthio radical attached through a sulfur atom to an alkyl radical.

[0049] The term "aroyl" is an aryl radical with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

[0050] The term "aryl", alone or in combination, is a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

[0051] The term "arylamino" is an amino group, which has been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

[0052] The term "aryloxyalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent oxygen atom.

[0053] The term "arylthioalkyl" is a radical having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

[0054] The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", is -(C=O)-.

[0055] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", is -CO2H.

[0056] The term "carboxyalkyl" is an alkyl radical substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which are lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl.

[0057] The term "corticotropin releasing factor" and "corticotropin releasing hormone" both refer to the same 41 amino acid polypeptide as described herein and are used interchangeably without consequence.

[0058] The term "corticotropin releasing factor antagonist" or alternatively "corticotropin releasing hormone antagonist" is any peptide or non-peptide substance that tends to nullify the action of corticotropin releasing factor or that binds to a cell receptor to which corticotropin releasing factor would otherwise be able to bind and does not elicit a biological response. Corticotropin releasing factor antagonists can include, for example, peptide and non-peptide antagonists, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems. Specific examples of such corticotropin releasing factor antagonists include, for example, α-helical CRF 9-41, antalarmin, CP-154,526, astressin, NBI 27914, and R121919. Furthermore, a corticotropin releasing factor antagonist may bind any of the corticotropin releasing factor receptors, including, for example, CRF_1, CRF_2, and CRF-BP receptors.

[0059] The term "cycloalkenyl" is a partially unsaturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl.

[0060] The term "cycloalkyl" is a saturated carbocyclic radical having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0061] The term "cyclooxygenase-2 selective inhibitor" is a compound able to selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Typically, it includes compounds that have a cyclooxygenase-2 IC_{50} of less than about 0.2 micro molar, and also have a selectivity ratio of cyclooxygenase-1 (COX-1) IC_{50} to cyclooxygenase-2 (COX-2) IC_{50} of at least about 5, more typically of at least about 50, and even more typically, of at least about 100. Moreover, the cyclooxygenase-2 selective inhibitors as

described herein have a cyclooxygenase-1 IC_{50} of greater than about 1 micro molar, and more preferably of greater than 10 micro molar. Inhibitors of the cyclooxygenase pathway in the metabolism of arachidonic acid used in the present method may inhibit enzyme activity through a variety of mechanisms. By the way of example, and without limitation, the inhibitors used in the methods described herein may block the enzyme activity directly by acting as a substrate for the enzyme.

[0062] The term "halo" is a halogen such as fluorine, chlorine, bromine or iodine.

[0063] The term "haloalkyl" is a radical wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically included are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" is a radical having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0064] The term "heteroaryl" is an unsaturated heterocyclyl radical. Examples of unsaturated heterocyclyl radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-

membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also includes radicals where heterocyclyl radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

[0065] The term "heterocyclyl" is a saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

[0066] The term "heterocyclylalkyl" is a saturated and partially unsaturated heterocyclyl-substituted alkyl radical, such as pyrrolidinylmethyl, and heteroaryl-substituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

[0067] The term "hydrido" is a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH2-) radical.

[0068] The term "hydroxyalkyl" is a linear or branched alkyl radical having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0069] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product; that is

the "pharmaceutically acceptable" material is relatively safe and/or non-toxic, though not necessarily providing a separable therapeutic benefit by itself. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzy1ethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[0070] The term "prodrug" refers to a chemical compound that can be converted into a therapeutic compound by metabolic or simple chemical processes within the body of the subject. For example, a class of prodrugs of COX-2 inhibitors is described in US Patent No. 5,932,598, herein incorporated by reference.

[0071] The term "subject" for purposes of treatment includes any human or animal subject who is need of treatment for an ischemic mediated central nervous system disorder or injury or who is at risk for developing an ischemic mediated central nervous system disorder or injury. The subject can be a domestic livestock species, a laboratory animal species, a zoo animal or a companion animal. In one embodiment, the subject is a mammal. In another embodiment, the mammal is a human being.

[0072] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, is a divalent radical $-SO_2-$. "Alkylsulfonyl" is an alkyl radical attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" are NH_2O_2S-.

[0073] The phrase "therapeutically-effective" is intended to qualify the amount of each agent (i.e. the amount of cyclooxygenase-2 selective inhibitor and the amount of corticotropin releasing factor antagonist) which will achieve the goal of improvement in disorder severity and the frequency of incidence over no treatment or treatment of each agent by itself.

[0074] The term "thrombotic event" or "thromboembolic event" includes, but is not limited to arterial thrombosis, including stent and graft thrombosis, cardiac thrombosis, coronary thrombosis, heart valve thrombosis, pulmonary thrombosis and venous thrombosis. Cardiac thrombosis is thrombosis in the heart. Pulmonary thrombosis is thrombosis in the lung. Arterial thrombosis is thrombosis in an artery. Coronary thrombosis is the development of an obstructive thrombus in a coronary artery, often causing sudden death or a myocardial infarction. Venous thrombosis is thrombosis in a vein. Heart valve thrombosis is a thrombosis on a heart valve. Stent thrombosis is thrombosis resulting from and/or located in the vicinity of a vascular stent. Graft thrombosis is thrombosis resulting from and/or located in the vicinity of an implanted graft, particularly a vascular graft. A thrombotic event as used herein is meant to embrace both a local thrombotic event and a distal thrombotic event occurring anywhere within the body (e.g., a thromboembolic event such as for example an embolic stroke).

[0075] The term "vaso-occlusive event" includes a partial occlusion (including a narrowing) or complete occlusion of a blood vessel, a stent or a vascular graft. A vaso-occlusive event intends to embrace thrombotic or thromboembolic events, and the vascular occlusion disorders or conditions to which they give rise. Thus, a vaso-occlusive event is intended to embrace all vascular occlusive disorders resulting in partial or total vessel occlusion from thrombotic or thromboembolic events.

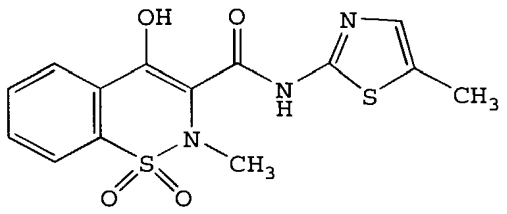
DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0076] The present invention provides a combination therapy comprising the administration to a subject of a therapeutically effective amount of a COX-2 selective inhibitor in combination with a therapeutically effective amount of a corticotropin releasing factor antagonist. The combination therapy is used to treat or prevent ischemic mediated central nervous system damage, such as damage to a central nervous system cell resulting from a decrease in blood flow to the cell or damage resulting from a traumatic injury to the cell. In addition, the combination therapy may

also be useful for the treatment of stroke or other vaso-occlusive events. When administered as part of a combination therapy, the COX-2 selective inhibitor together with the corticotropin releasing factor antagonist provide enhanced treatment options as compared to administration of the COX-2 selective inhibitor or the corticotropin releasing factor antagonist alone.

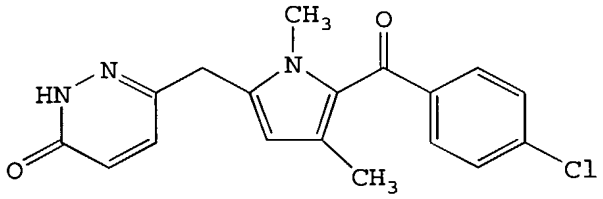
CYCLOOXYGENASE-2 SELECTIVE INHIBITORS

[0077] A number of suitable cyclooxygenase-2 selective inhibitors or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof, may be employed in the composition of the current invention. In one embodiment, the cyclooxygenase-2 selective inhibitor can be, for example, the cyclooxygenase-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-1.



B-1

[0078] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is the cyclooxygenase-2 selective inhibitor, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3) or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having Formula B-2.

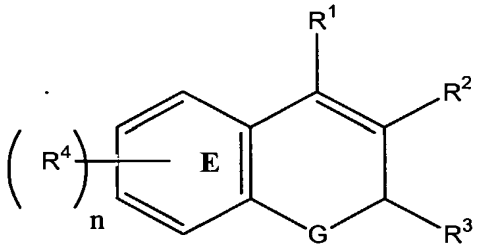


B-2

[0079] In still another embodiment the cyclooxygenase-2 selective inhibitor is a chromene compound that is a substituted benzopyran or a substituted benzopyran analog, and even more typically, selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, dihydronaphthalenes or a compound having

[0080] Formula *I* shown below and possessing, by way of example and not limitation, the structures disclosed in Table 1. Furthermore, benzopyran cyclooxygenase-2 selective inhibitors useful in the practice of the present methods are described in U.S. Patent No. 6,034,256 and 6,077,850 herein incorporated by reference in their entirety.

[0081] In another embodiment, the cyclooxygenase-2 selective inhibitor is a chromene compound represented by Formula *I* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(I)

[0082] wherein:

[0083] n is an integer which is 0, 1, 2, 3 or 4;

[0084] G is O, S or NR^a;

[0085] R^a is alkyl;

[0086] R^1 is selected from the group consisting of H and aryl;

[0087] R^2 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0088] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0089] each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0090] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0091] wherein:

[0092] n is an integer which is 0, 1, 2, 3 or 4;

[0093] G is O, S or NR^a;

[0094] R^a is alkyl;

[0095] R^1 is H;

[0096] R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

[0097] R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

[0098] each R^4 is independently selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0099] In a further embodiment, the cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)*, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0100] wherein:

[0101] n is an integer which is 0, 1, 2, 3 or 4;

[0102] G is oxygen or sulfur;

[0103] R^1 is H;

[0104] R^2 is carboxyl, lower alkyl, lower aralkyl or lower alkoxycarbonyl;

[0105] R^3 is lower haloalkyl, lower cycloalkyl or phenyl; and

[0106] each R^4 is independently H, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower

alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0107] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0108] wherein:

[0109] n is an integer which is 0, 1, 2, 3 or 4;

[0110] G is oxygen or sulfur;

[0111] R^1 is H;

[0112] R^2 is carboxyl;

[0113] R^3 is lower haloalkyl; and

[0114] each R^4 is independently H, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, or lower alkylcarbonyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0115] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0116] wherein:

[0117] n is an integer which is 0, 1, 2, 3 or 4;

[0118] G is oxygen or sulfur;

[0119] R^1 is H;

[0120] R^2 is carboxyl;

[0121] R^3 is fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, or trifluoromethyl; and

[0122] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-

methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0123] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0124] wherein:

[0125] n is an integer which is 0, 1, 2, 3 or 4;

[0126] G is oxygen or sulfur;

[0127] R^1 is H;

[0128] R^2 is carboxyl;

[0129] R^3 is trifluoromethyl or pentafluoroethyl; and

[0130] each R^4 is independently H, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, or phenyl; or wherein R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical.

[0131] In yet another embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound having the structure of Formula *(I)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0132] wherein:

[0133] n is 4;

[0134] G is O or S;

[0135] R^1 is H;

[0136] R^2 is CO_2H;

[0137] R^3 is lower haloalkyl;

[0138] a first R^4 corresponding to R^9 is hydrido or halo;

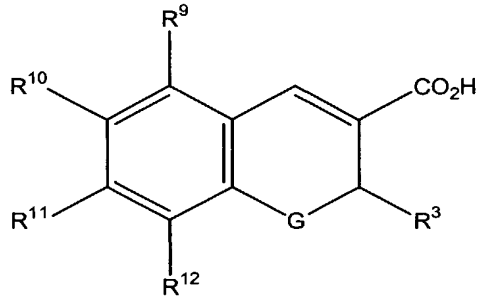
[0139] a second R^4 corresponding to R^{10} is H, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-

membered nitrogen-containing heterocyclosulfonyl, or 6- membered nitrogen-containing heterocyclosulfonyl;

[0140] a third R^4 corresponding to R^{11} is H, lower alkyl, halo, lower alkoxy, or aryl; and

[0141] a fourth R^4 corresponding to R^{12} is H, halo, lower alkyl, lower alkoxy, or aryl;

[0142] wherein Formula *(I)* is represented by Formula *(Ia)*:



(Ia)

[0143] The cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can also be a compound of having the structure of Formula *(Ia)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0144] wherein:

[0145] G is O or S;

[0146] R^3 is trifluoromethyl or pentafluoroethyl;

[0147] R^9 is H, chloro, or fluoro;

[0148] R^{10} is H, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, or morpholinosulfonyl;

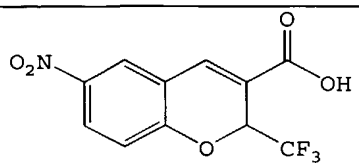
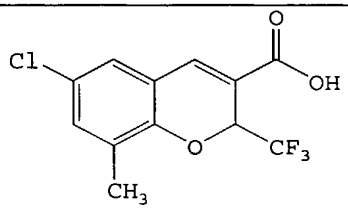
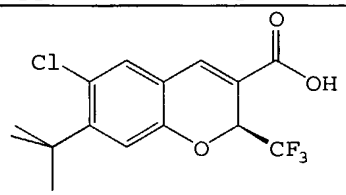
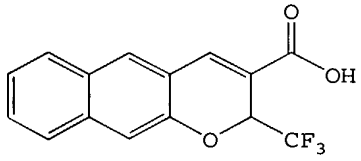
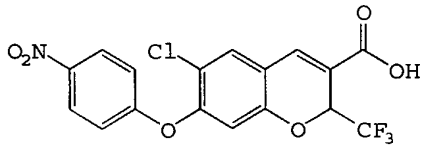
[0149] R^{11} is H, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, or phenyl; and

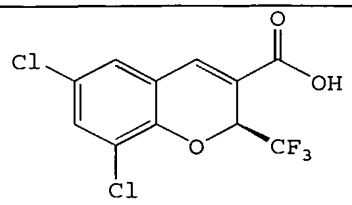
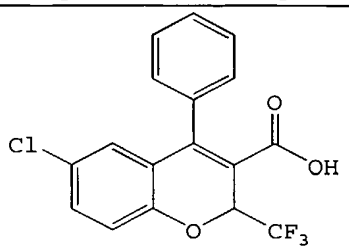
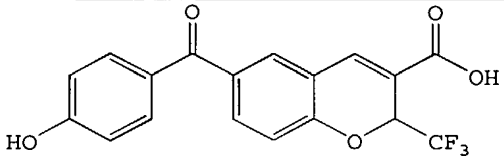
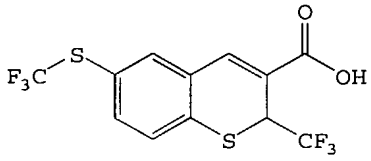
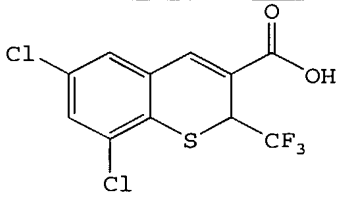
[0150] R^{12} is H, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, or phenyl.

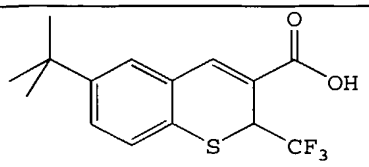
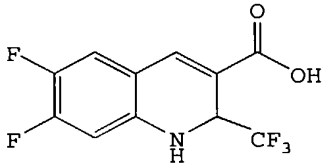
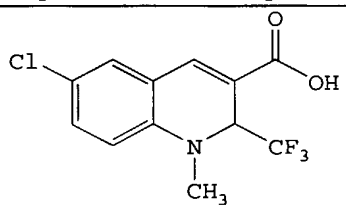
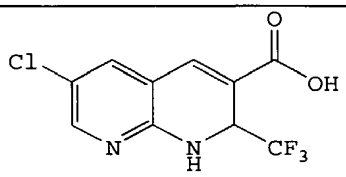
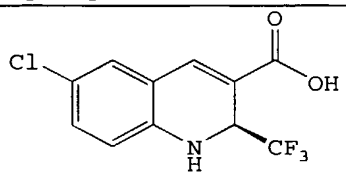
[0151] Examples of exemplary chromene cyclooxygenase-2 selective inhibitors are depicted in Table 1 below.

TABLE 1

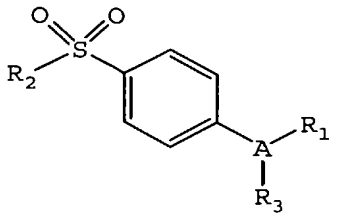
EXAMPLES OF CHROMENE CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1- benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

[0152] In a further embodiment, the cyclooxygenase-2 selective inhibitor is selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *II* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof,



II

[0153] wherein:

[0154] A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

[0155] R_1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R_1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0156] R_2 is selected from the group consisting of methyl and amino; and

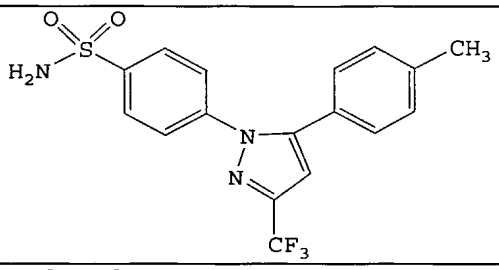
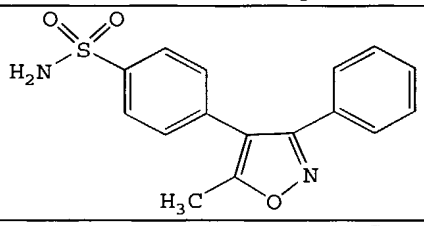
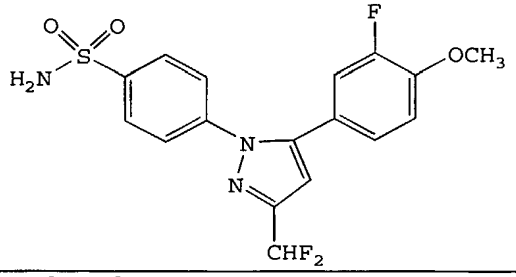
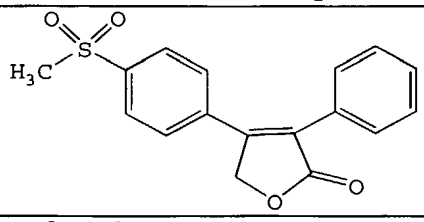
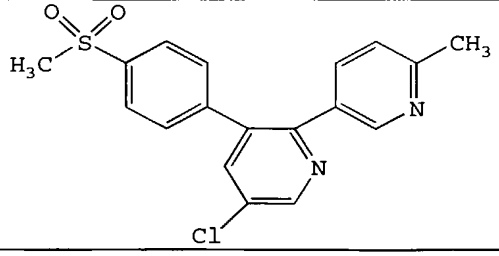
[0157] R_3 is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl.

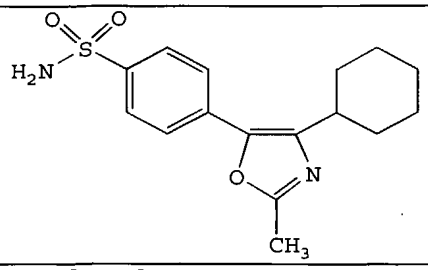
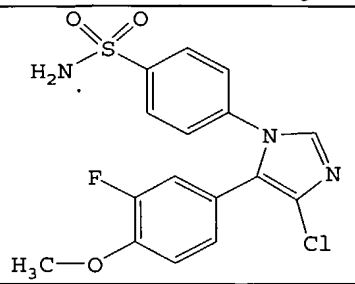
[0158] In another embodiment, the cyclooxygenase-2 selective inhibitor represented by the above Formula *II* is selected from the group of compounds illustrated in Table 2, consisting of celecoxib (B-18; U.S. Patent No. 5,466,823; CAS No. 169590-42-5), valdecoxib (B-19; U.S. Patent No. 5,633,272; CAS No. 181695-72-7),

deracoxib (B-20; U.S. Patent No. 5,521,207; CAS No. 169590-41-4), rofecoxib (B-21; CAS No. 162011-90-7), etoricoxib (MK-663; B-22; PCT publication WO 98/03484), tilmacoxib (JTE-522; B-23; CAS No. 180200-68-4), and cimicoxib (UR-8880; B23a; CAS No. 265114-23-6).

TABLE 2

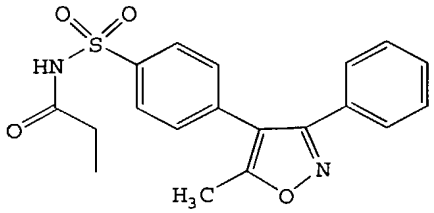
EXAMPLES OF TRICYCLIC CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

Compound Number	**Structural Formula**
B-18	
B-19	
B-20	
B-21	
B-22	

Compound Number	Structural Formula
B-23	
B23a	

[0159] In still another embodiment, the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

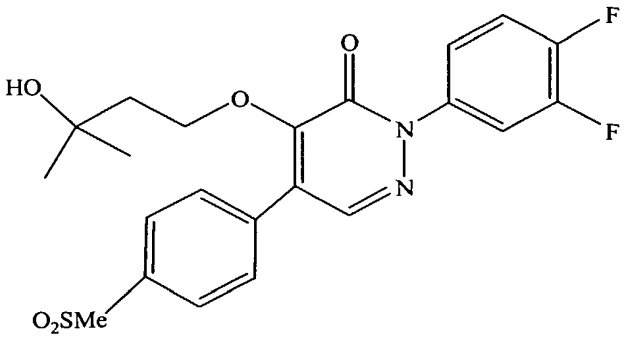
[0160] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is parecoxib (B-24, U.S. Patent No. 5,932,598, CAS No. 198470-84-7), which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (US 5,932,598, herein incorporated by reference).



B-24

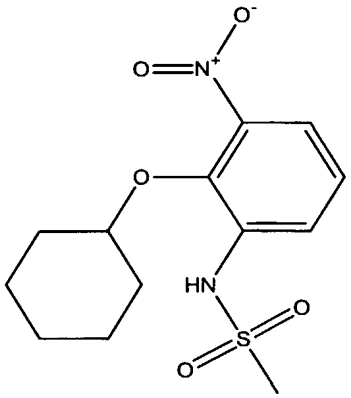
[0161] One form of parecoxib is sodium parecoxib.

[0162] In another embodiment of the invention, the compound having the formula B-25 or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-25 that has been previously described in International Publication number WO 00/24719 (which is herein incorporated by reference) is another tricyclic cyclooxygenase-2 selective inhibitor that may be advantageously employed.



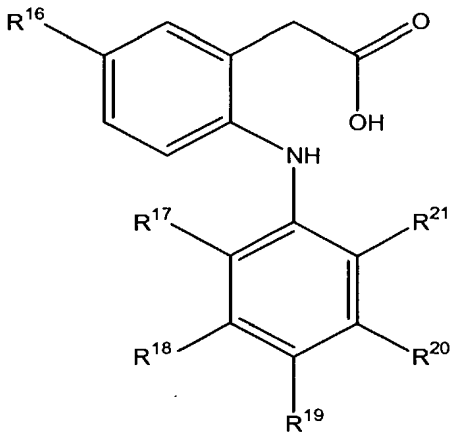
B-25

[0163] Another cyclooxygenase-2 selective inhibitor that is useful in connection with the method(s) of the present invention is N-(2-cyclohexyloxynitrophenyl)-methane sulfonamide (NS-398) having a structure shown below as B-26, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug of a compound having formula B-26.



B-26

[0164] In yet a further embodiment, the cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(III)

[0165] wherein:

[0166] R^{16} is methyl or ethyl;

[0167] R^{17} is chloro or fluoro;

[0168] R^{18} is hydrogen or fluoro;

[0169] R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

[0170] R^{20} is hydrogen or fluoro; and

[0171] R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17}, R^{18}, R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H.

[0172] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor used in connection with the method(s) of the present invention is a compound that has the designation of COX 189 (lumiracoxib; B-211) and that has the structure shown in Formula *(III)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof wherein:

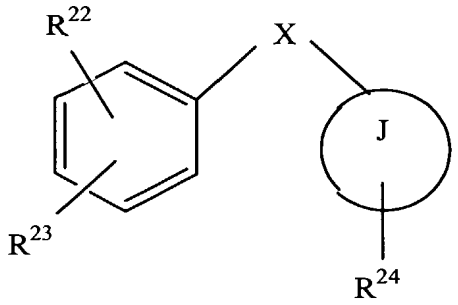
[0173] R^{16} is ethyl;

[0174] R^{17} and R^{19} are chloro;

[0175] R^{18} and R^{20} are hydrogen; and

[0176] R^{21} is methyl.

[0177] In yet another embodiment, the cyclooxygenase-2 selective inhibitor is represented by Formula *(IV)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(IV)

[0178] wherein:

[0179] X is O or S;

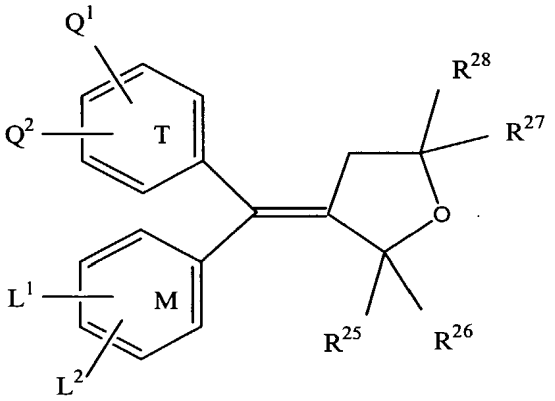
[0180] J is a carbocycle or a heterocycle;

[0181] R^{22} is $NHSO_2CH_3$ or F;

[0182] R^{23} is H, NO_2, or F; and

[0183] R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

[0184] According to another embodiment, the cyclooxygenase-2 selective inhibitors used in the present method(s) have the structural Formula *(V)* or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof:



(V)

[0185] wherein:

[0186] T and M are independently phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0187] R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or

[0188] R^{25} and R^{26}, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or

[0189] $R^{27}$and R^{28}, together with the carbon atom to which they are attached, form a carbonyl or a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0190] Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, lower methoxy having from 1 to 6 carbon atoms, alkylsulfinyl or alkylsulfonyl; and

[0191] at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or Q^1 and Q^2 together form methylenedioxy; or L^1 and L^2 together form methylenedioxy.

[0192] In another embodiment, the compounds N-(2-cyclohexyloxynitrophenyl) methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide or isomers, pharmaceutically acceptable salts, esters, or prodrugs thereof having the structure of Formula *(V)* are employed as cyclooxygenase-2 selective inhibitors.

[0193] In a further embodiment, compounds that are useful for the cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof used in connection with the method(s) of the present invention, the structures for which are set forth in Table 3 below, include, but are not limited to:

[0194] 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

[0195] 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

[0196] 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

[0197] 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

[0198] 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

[0199] 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

[0200] 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

[0201] 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

[0202] 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

[0203] 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

[0204] 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

[0205] 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

[0206] 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

[0207] 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

[0208] 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

[0209] 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

[0210] 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

[0211] 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

[0212] 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

[0213] 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

[0214] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

[0215] 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

[0216] 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

[0217] 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

[0218] 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

[0219] 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

[0220] 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

[0221] 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

[0222] 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

[0223] 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

[0224] 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

[0225] 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

[0226] 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

[0227] 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

[0228] 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

[0229] 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

[0230] 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

[0231] 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

[0232] 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

[0233] 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

[0234] 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

[0235] 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

[0236] 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

[0237] 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

[0238] 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

[0239] 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

[0240] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

[0241] 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

[0242] 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a) pyridine (B-75);

[0243] 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

[0244] 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

[0245] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

[0246] 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-79);

[0247] 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-80);

[0248] 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl) benzenesulfonamide (B-81);

[0249] 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-82);

[0250] 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-83);

[0251] 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-84);

[0252] 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl) benzenesulfonamide (B-85);

[0253] 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

[0254] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-87);

[0255] 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-88);

[0256] 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-89);

[0257] 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-90);

[0258] 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-91);

[0259] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-92);

[0260] 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-93);

[0261] 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-94);

[0262] 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl] benzenesulfonamide (B-95);

[0263] 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-96);

[0264] 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-97);

[0265] 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-98);

[0266] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-99);

[0267] 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

[0268] 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-101);

[0269] 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (B-102);

[0270] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-

[0271] 5-ene (B-103);

[0272] 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-104);

[0273] 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-

[0274] 6-ene (B-105);

[0275] 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl) phenyl]spiro [2.4]hept-5-ene (B-106);

[0276] 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-107);

[0277] 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro [2.4]hept-5-ene (B-108);

[0278] 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene (B-109);

[0279] 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl] benzenesulfonamide (B-110);

[0280] 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-111);

[0281] 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl phenyl)thiazole (B-112);

[0282] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);

[0283] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);

[0284] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);

[0285] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);

[0286] 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino) thiazole (B-117);

[0287] 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methyl sulfonyl)phenyl]thiazole (B-118);

[0288] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

[0289] 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

[0290] 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide (B-121);

[0291] 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

[0292] 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl] benzenesulfonamide (B-123);

[0293] 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

[0294] 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

[0295] 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

[0296] 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-127);

[0297] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-128);

[0298] 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-129);

[0299] 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl] pyridine (B-130);

[0300] 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-

[0301] 2-yl]pyridine (B-131);

[0302] 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

[0303] 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

[0304] 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-134);

[0305] 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

[0306] 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-136);

[0307] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

[0308] 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

[0309] 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

[0310] 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoro methyl)-1H-imidazole (B-140);

[0311] 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

[0312] 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

[0313] 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-143);

[0314] 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoro methyl)-1H-imidazole (B-144);

[0315] 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

[0316] 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

[0317] 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzene sulfonamide (B-147);

[0318] 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

[0319] 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-149);

[0320] 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-150);

[0321] 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl] benzenesulfonamide (B-151);

[0322] 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoro methyl)-1H-pyrazole (B-152);

[0323] 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide (B-153);

[0324] N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

[0325] ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

[0326] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

[0327] 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

[0328] 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

[0329] 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

[0330] 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

[0331] 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

[0332] 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

[0333] 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

[0334] 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

[0335] 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

[0336] 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

[0337] 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

[0338] 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

[0339] 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

[0340] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

[0341] 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

[0342] 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-172);

[0343] 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-173);

[0344] 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-174);

[0345] 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-175);

[0346] 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-176);

[0347] 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methyl sulfonyl)benzene (B-177);

[0348] 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-178);

[0349] 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-179);

[0350] 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-180);

[0351] 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzene sulfonamide (B-181);

[0352] 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);

[0353] 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);

[0354] 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-184);

[0355] 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-185);

[0356] 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl] benzenesulfonamide (B-186);

[0357] 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl) benzene (B-187);

[0358] 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl] benzenesulfonamide (B-188);

[0359] 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);

[0360] ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);

[0361] 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl] acetic acid (B-191);

[0362] 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] oxazole (B-192);

[0363] 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);

[0364] 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);

[0365] 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-195);

[0366] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);

[0367] 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);

[0368] 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);

[0369] 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

[0370] 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-200);

[0371] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide (B-201);

[0372] 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);

[0373] 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);

[0374] 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);

[0375] 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide (B-205);

[0376] 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);

[0377] 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);

[0378] [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl] benzenesulfonamide (B-208);

[0379] 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);

[0380] 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl] benzenesulfonamide (B-210);

[0381] [2-(2-chloro-6-fluoro-phenylamino)-5-methyl-phenyl]-acetic acid or COX 189 (lumiracoxib; B-211);

[0382] N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);

[0383] N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);

[0384] N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, sodium salt (B-214);

[0385] N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide (B-215);

[0386] 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one (B-216);

[0387] (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] methylene]-4(5H)-thiazolone (B-217);

[0388] CS-502 (B-218);

[0389] LAS-34475 (B-219);

[0390] LAS-34555 (B-220);

[0391] S-33516 (B-221);

[0392] SD-8381 (B-222);

[0393] L-783003 (B-223);

[0394] N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide (B-224);

[0395] D-1367 (B-225);

[0396] L-748731 (B-226);

[0397] (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid (B-227);

[0398] CGP-28238 (B-228);

[0399] 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

[0400] GR-253035 (B-230);

[0401] 6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

[0402] S-2474 (B-232);

[0403] 4-[4-(methyl)-sulfonyl)phenyl]-3-phenyl-2(5H)-furanone;

[0404] 4-(5-methyl-3-phenyl-4-isoxazolyl);

[0405] 2-(6-methylpyrid-3-yl)-3-(4-methylsulfonylphenyl)-5-chloropyridine;

[0406] 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl];

[0407] N-[[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl];

[0408] 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-

[0409] 1-yl]benzenesulfonamide;

[0410] (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid;

[0411] 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methyl sulfonyl)phenyl]-3(2H)-pyridzainone;

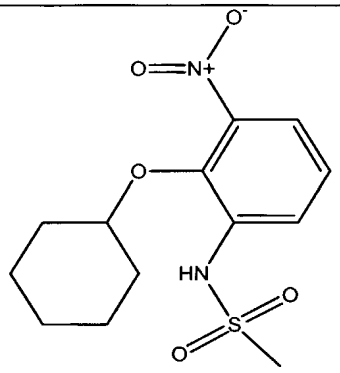
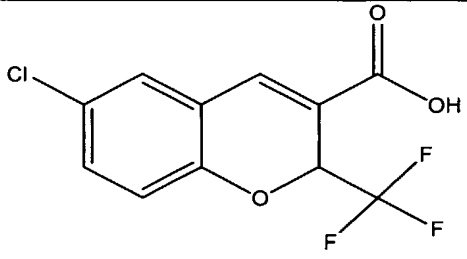
[0412] 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

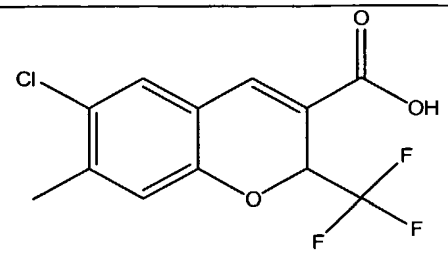
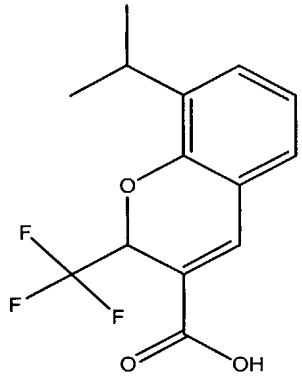
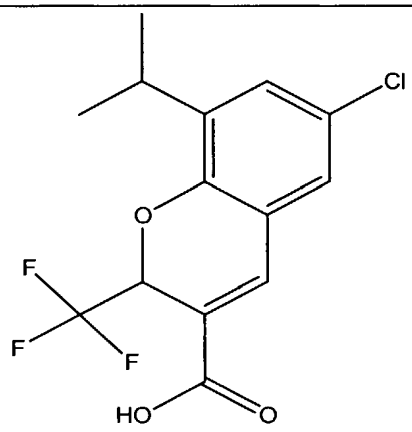
[0413] 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

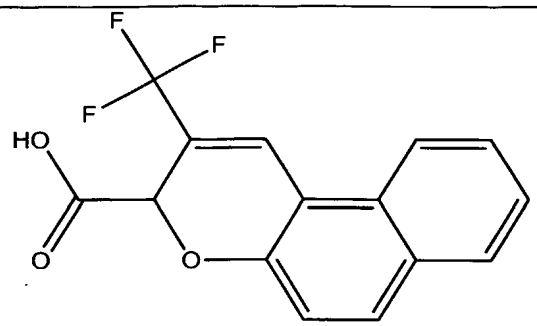
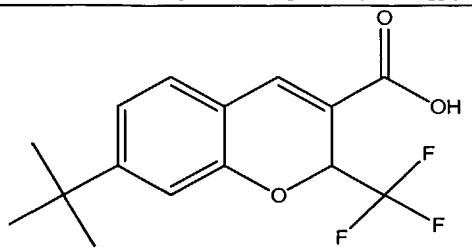
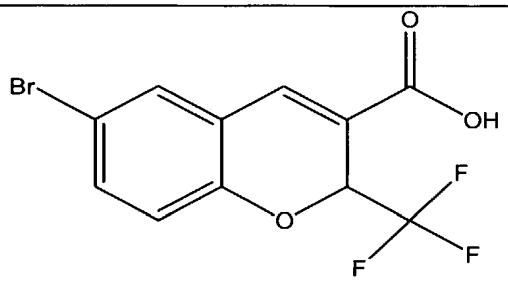
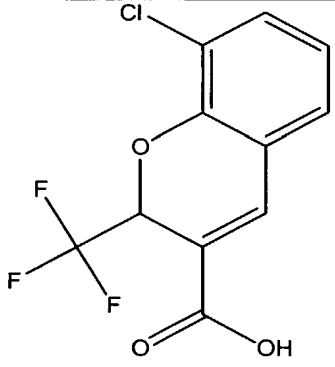
[0414] [2-(2,4-dichloro-6-ethyl-3,5-dimethyl-phenylamino)-5-propyl-phenyl]-acetic acid.

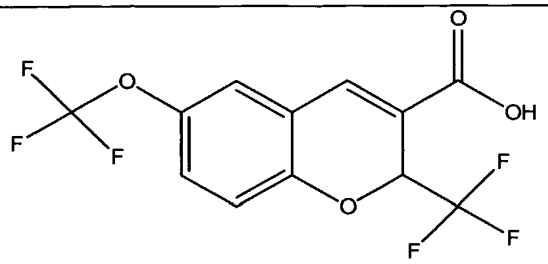
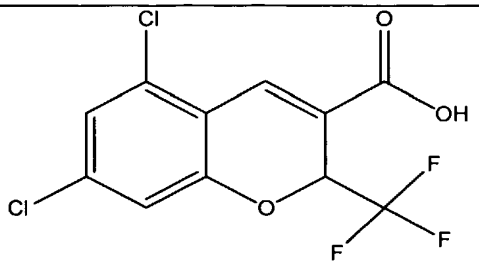
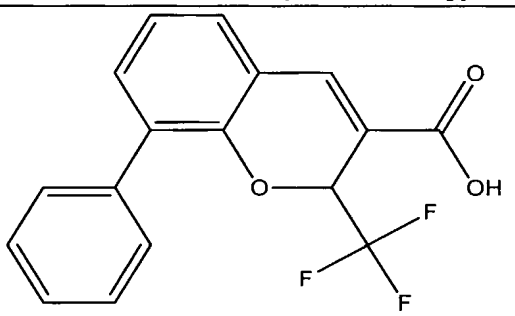
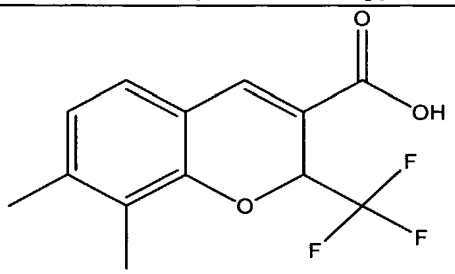
TABLE 3

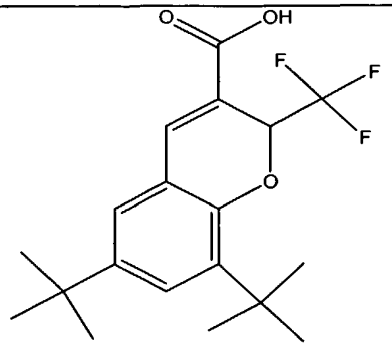
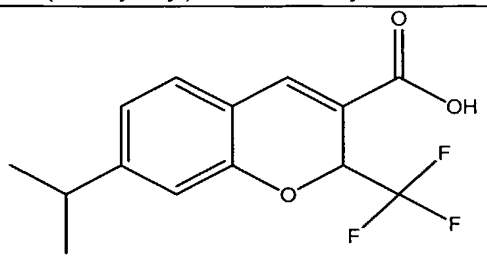
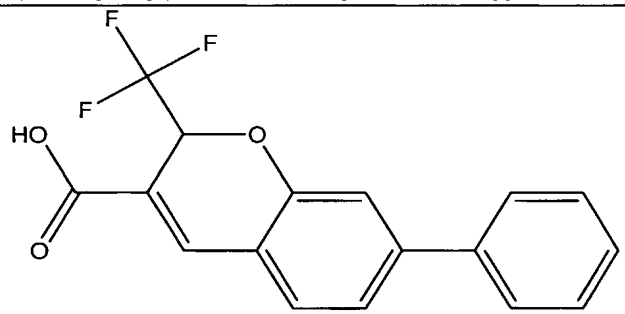
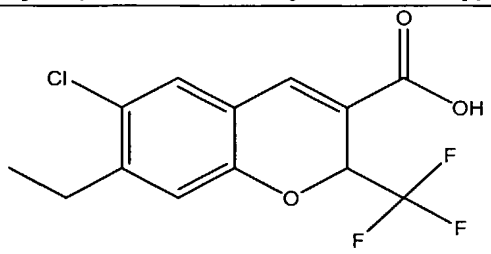
EXAMPLES OF CYCLOOXYGENASE-2 SELECTIVE INHIBITORS AS EMBODIMENTS

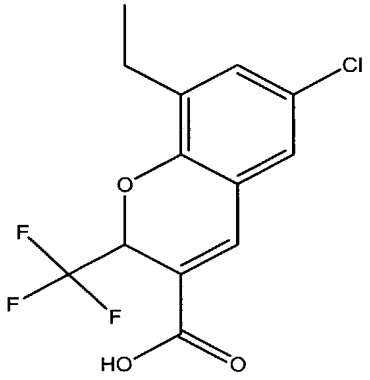
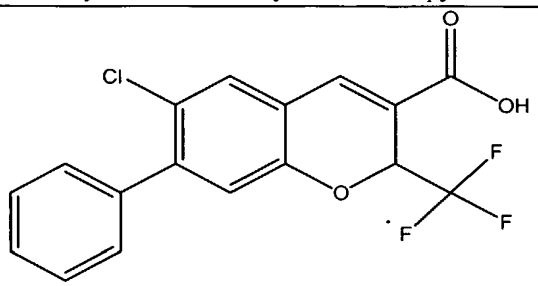
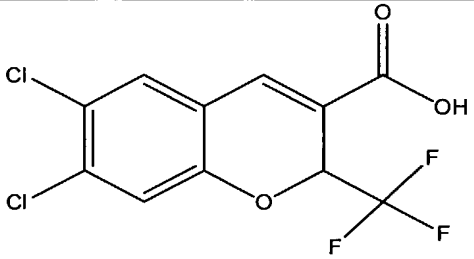
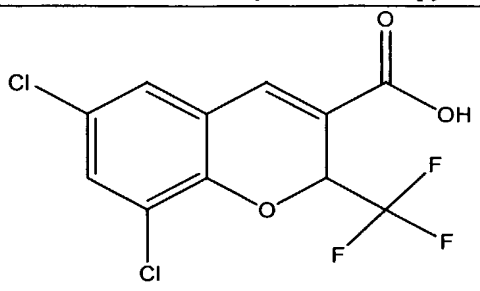
Compound Number	**Structural Formula**
B-26	 N-(2-cyclohexyloxynitrophenyl) methane sulfonamide or NS-398;
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

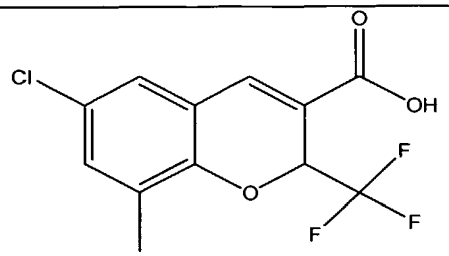
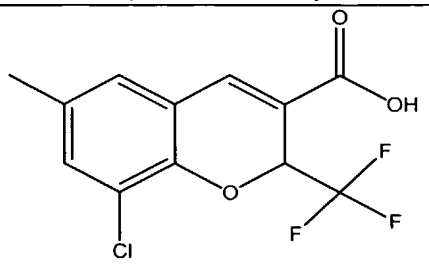
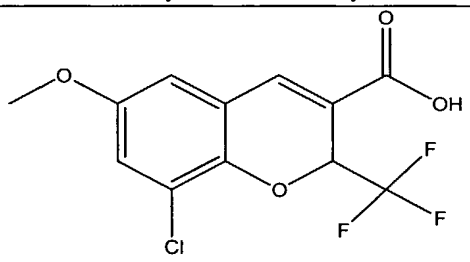
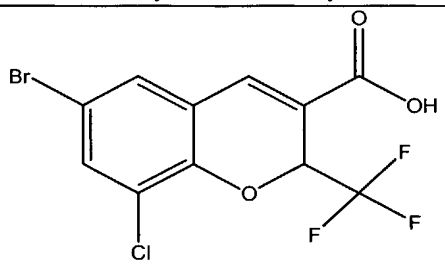
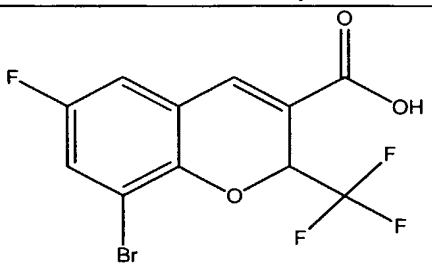
Compound Number	Structural Formula
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;

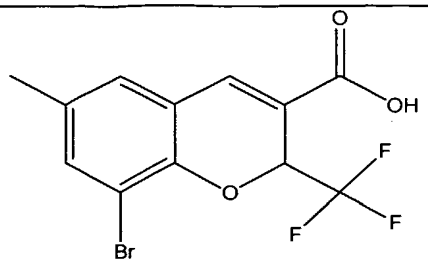
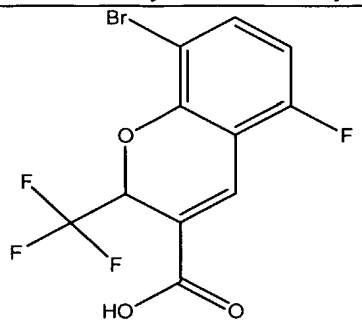
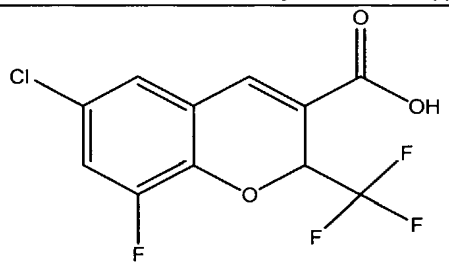
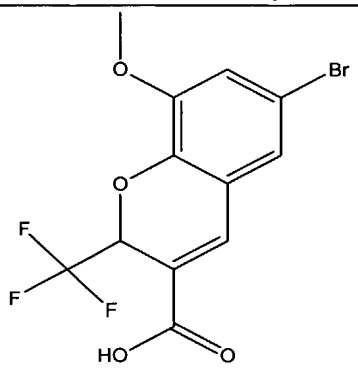
Compound Number	Structural Formula
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

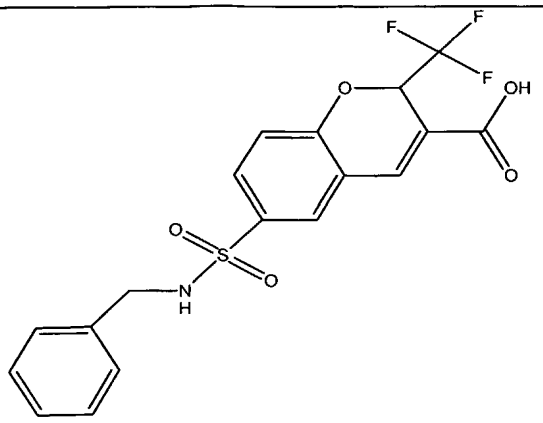
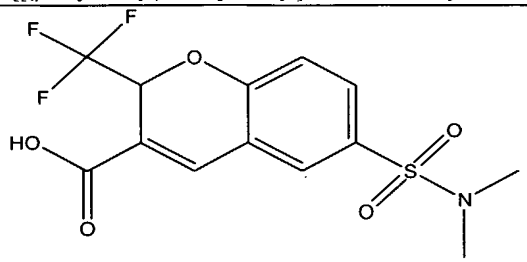
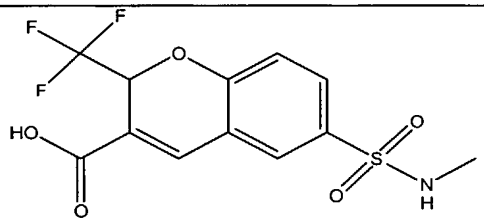
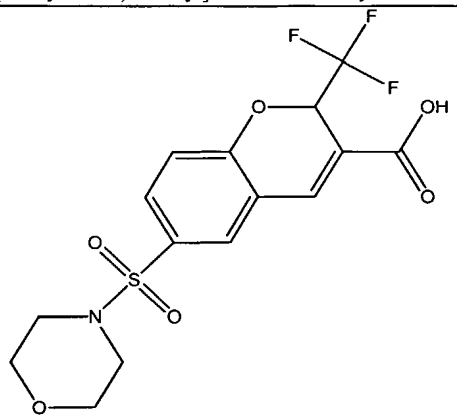
Compound Number	Structural Formula
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

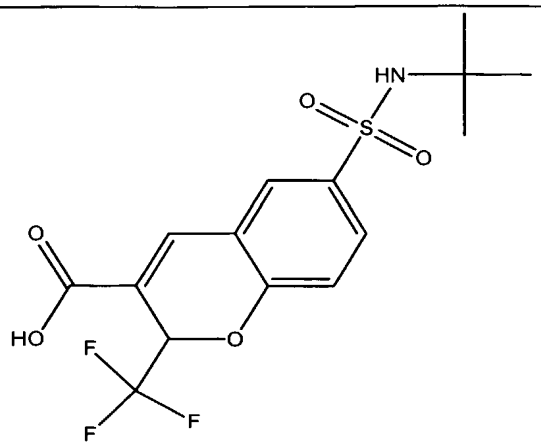
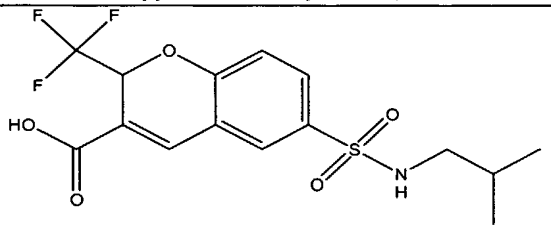
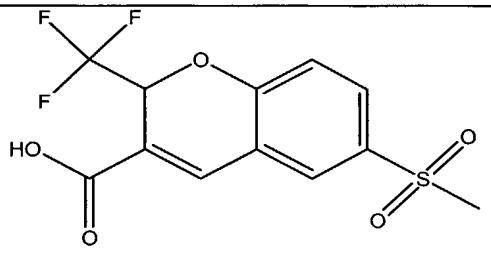
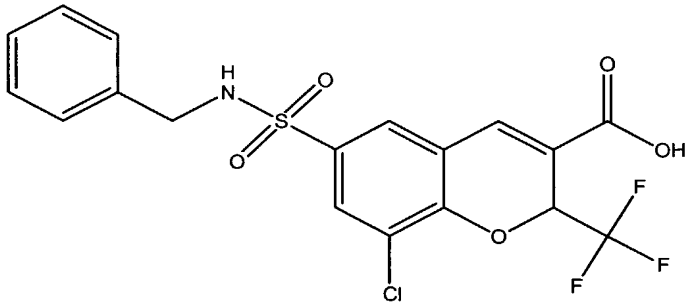
Compound Number	Structural Formula
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

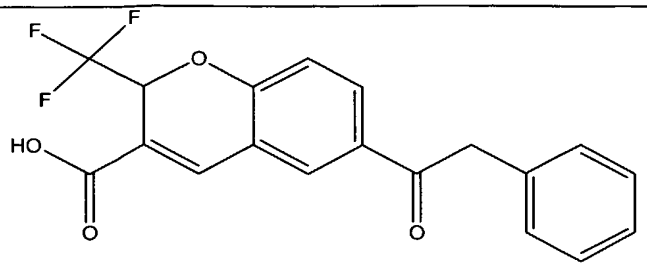
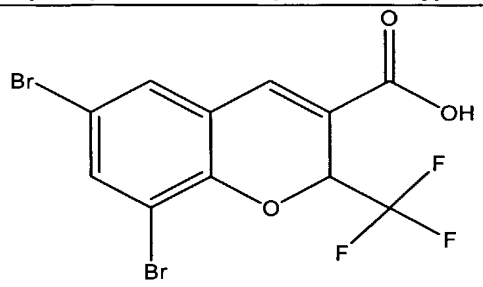
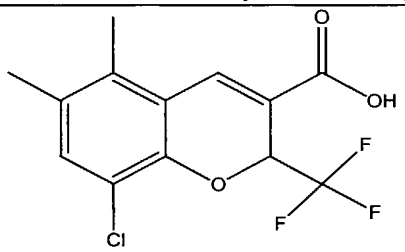
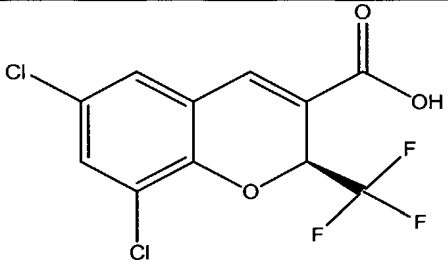
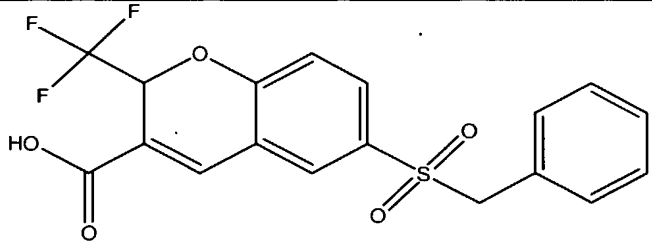
Compound Number	Structural Formula
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

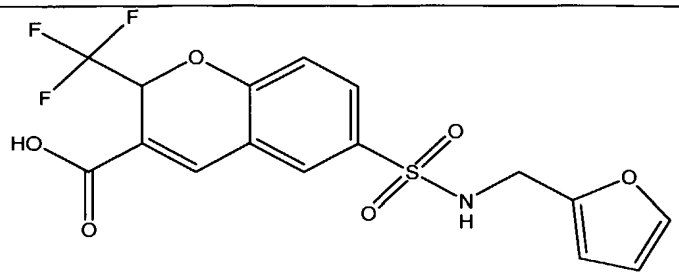
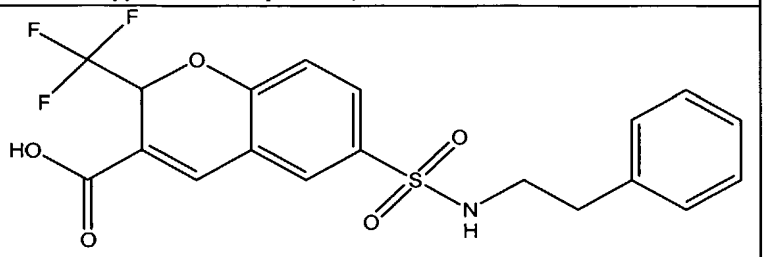
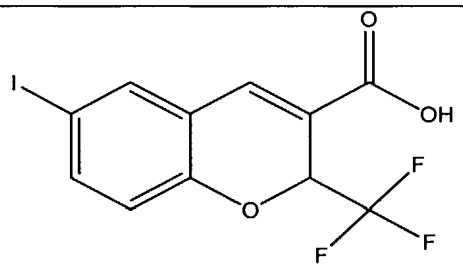
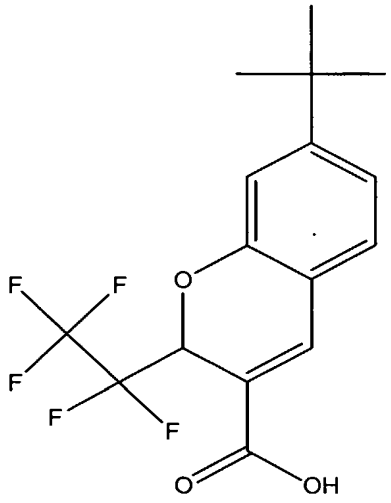
Compound Number	Structural Formula
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

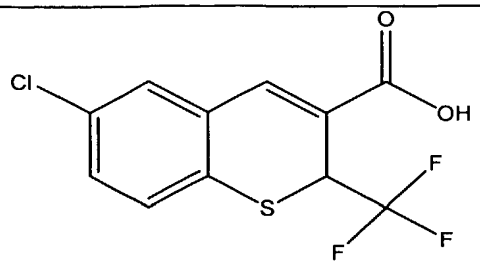
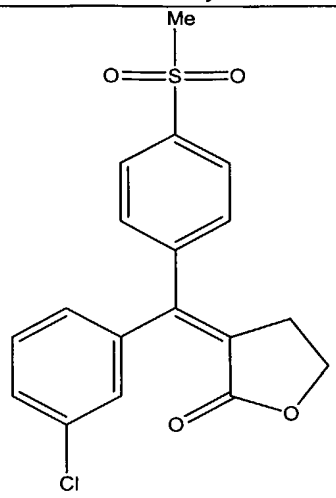
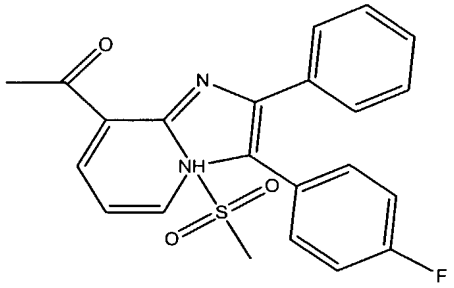
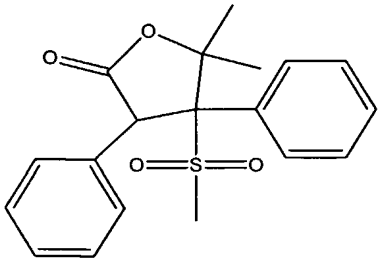
Compound Number	Structural Formula
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

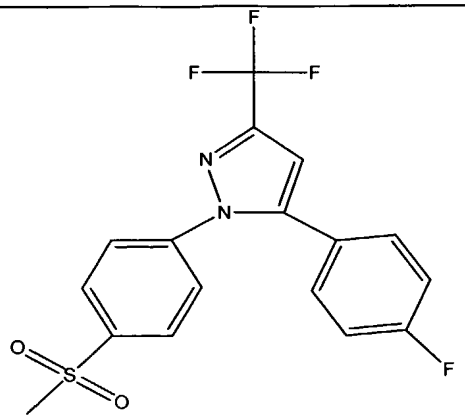
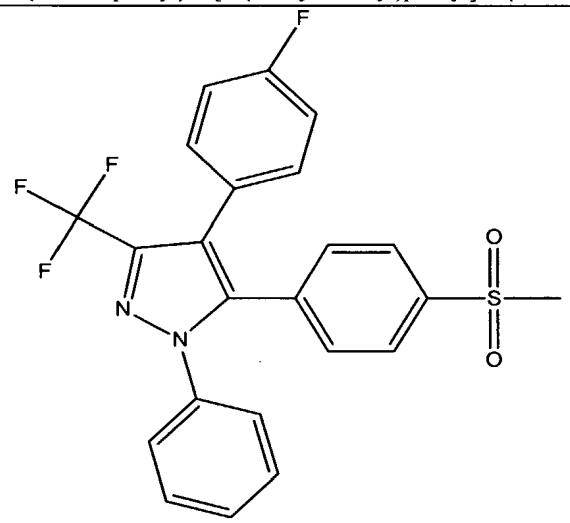
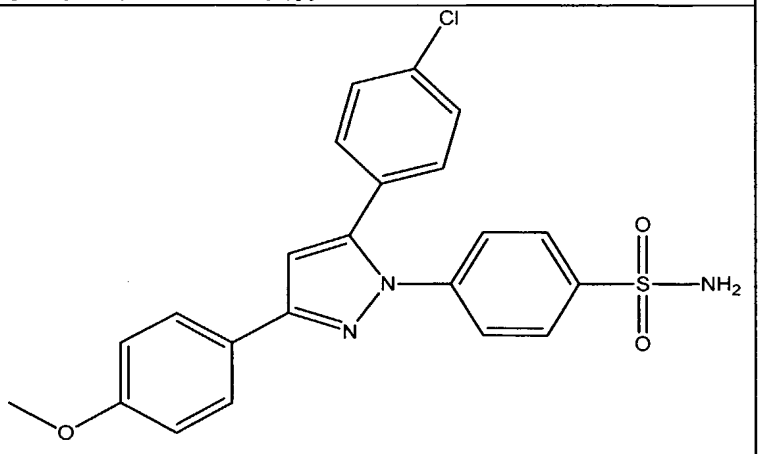
Compound Number	Structural Formula
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

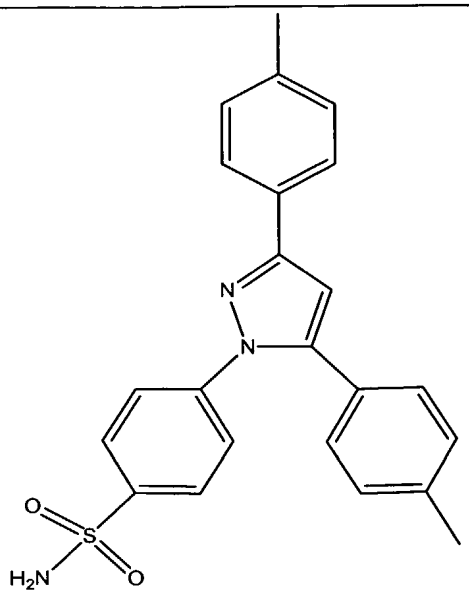
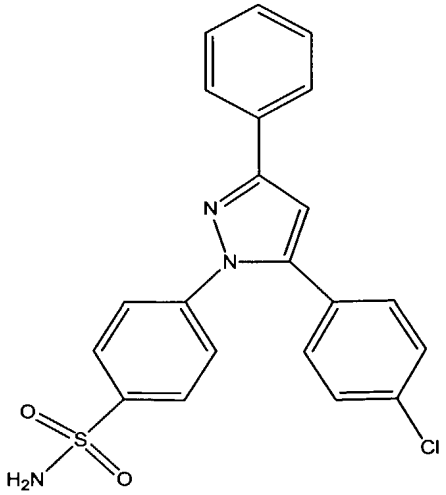
Compound Number	Structural Formula
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl- 2H-1-benzopyran-3-carboxylic acid;

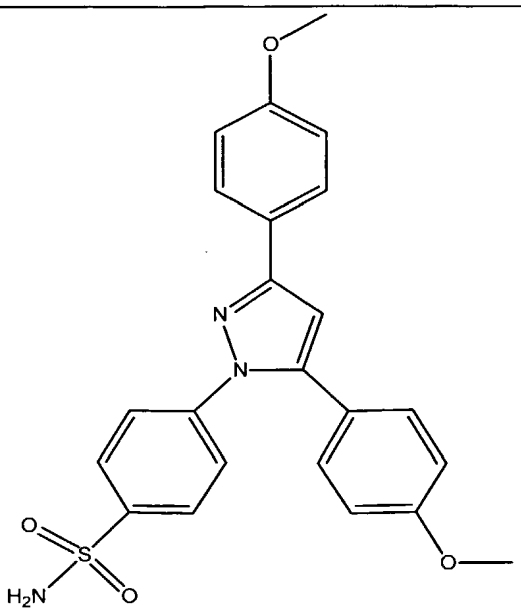
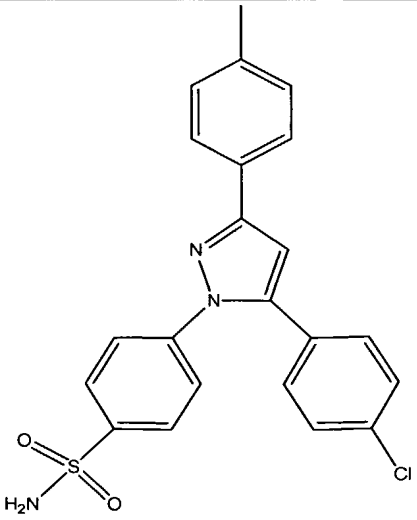
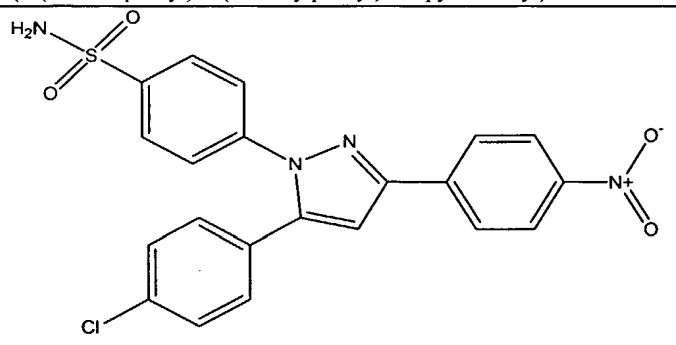
Compound Number	Structural Formula
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

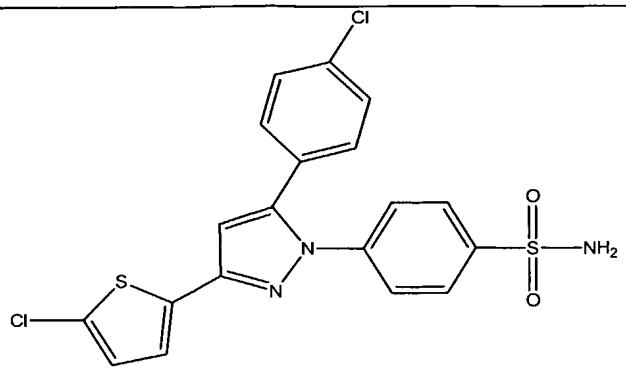
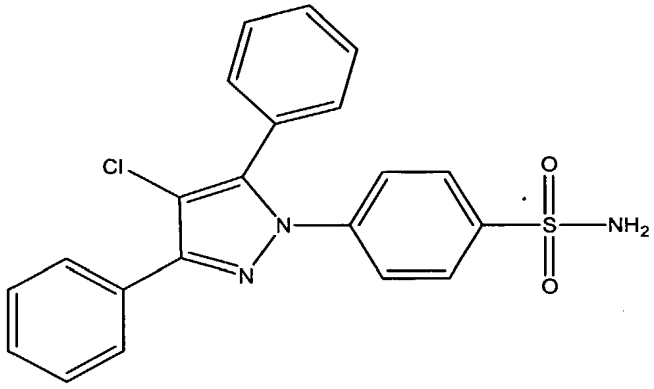
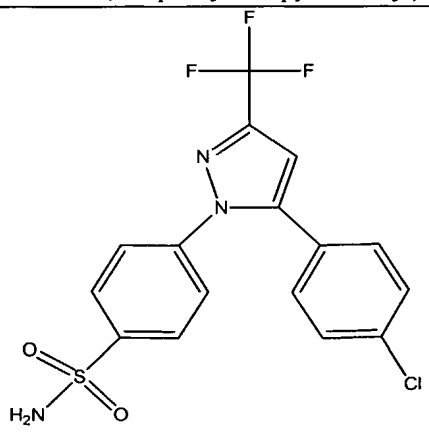
Compound Number	Structural Formula
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid;
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran -3-carboxylic acid;
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H -1-benzopyran-3-carboxylic acid;

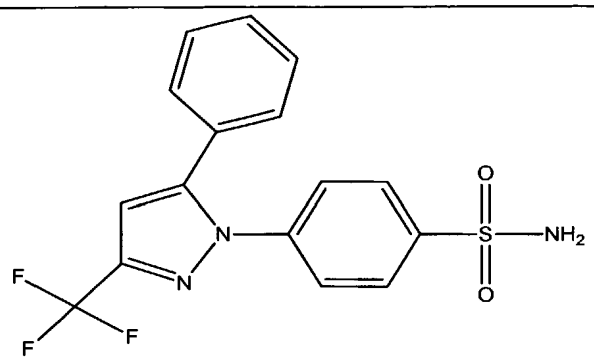
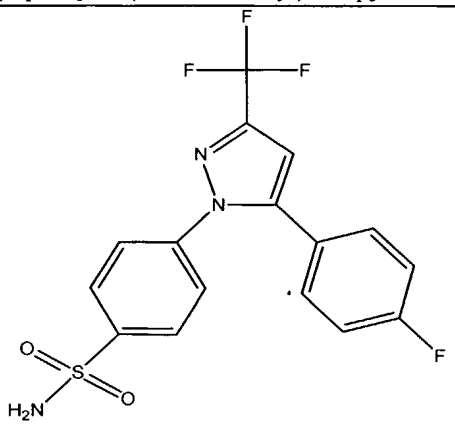
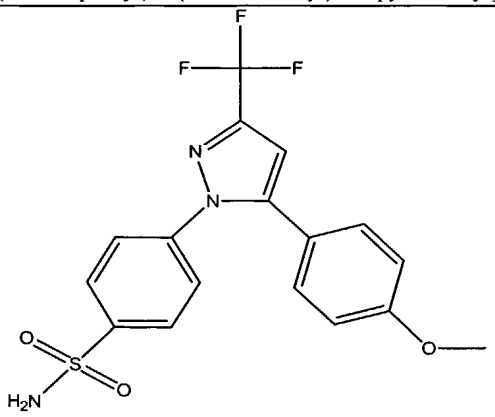
Compound Number	Structural Formula
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-74	 3-[(3-chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene] -dihydro-furan-2-one or BMS-347070;
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

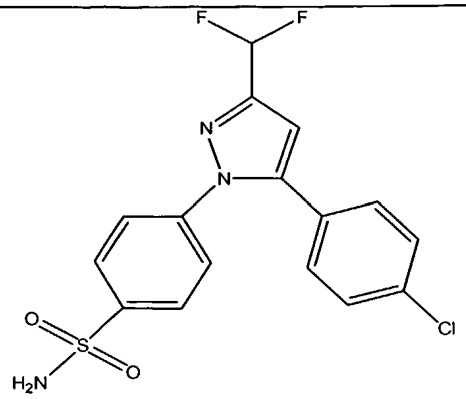
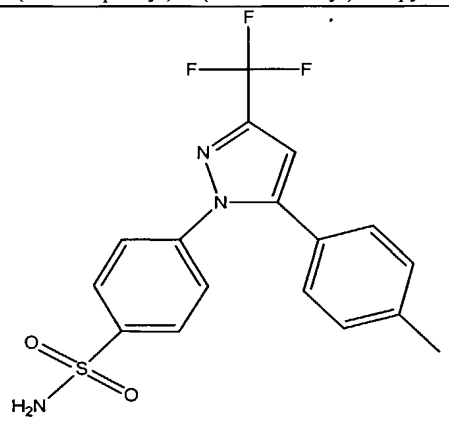
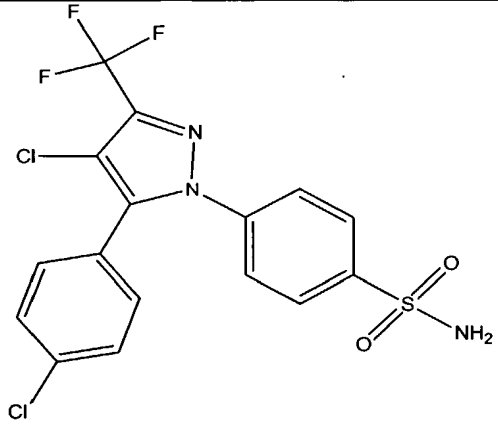
Compound Number	Structural Formula
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl) benzenesulfonamide;

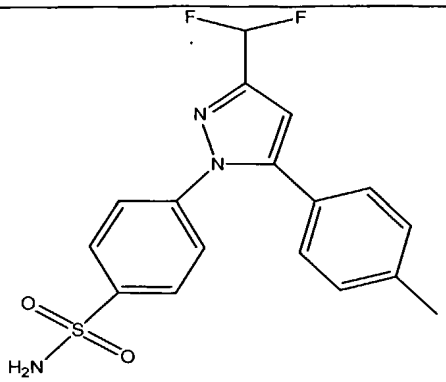
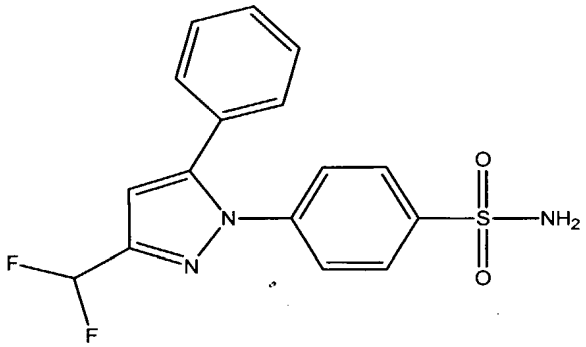
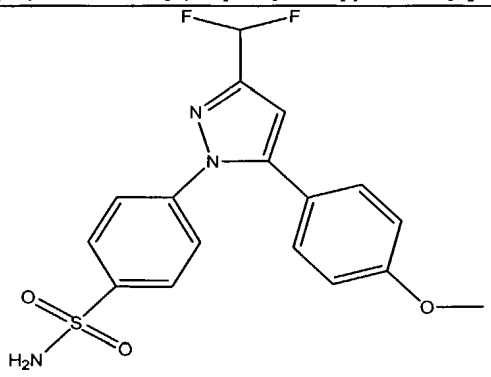
Compound Number	Structural Formula
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

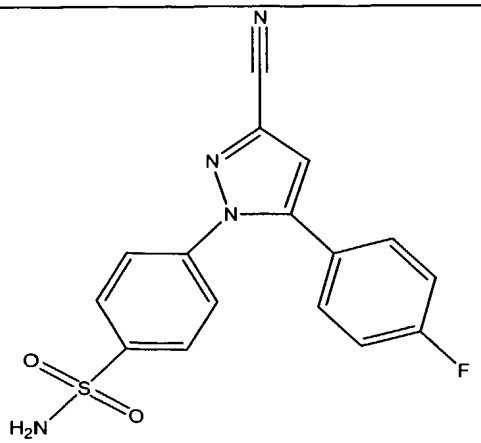
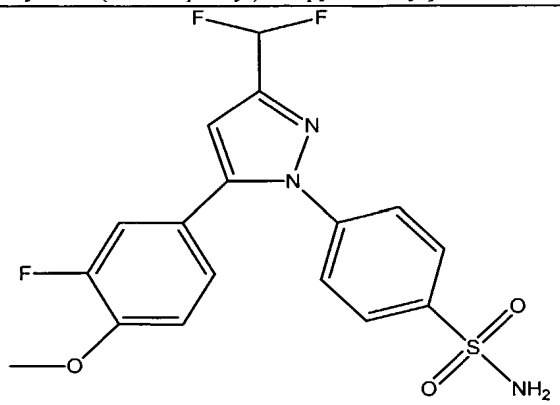
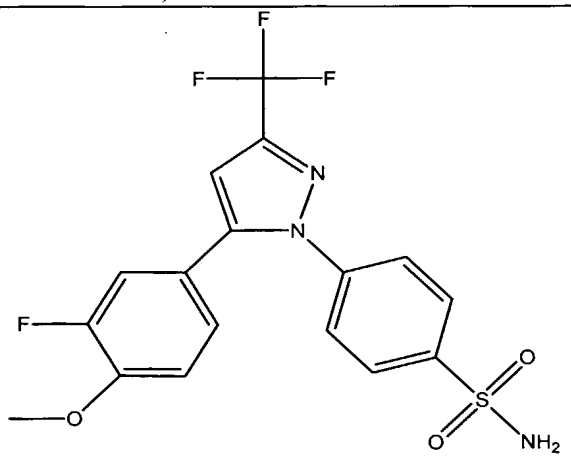
Compound Number	Structural Formula
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

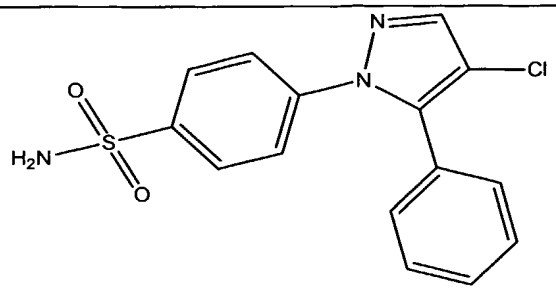
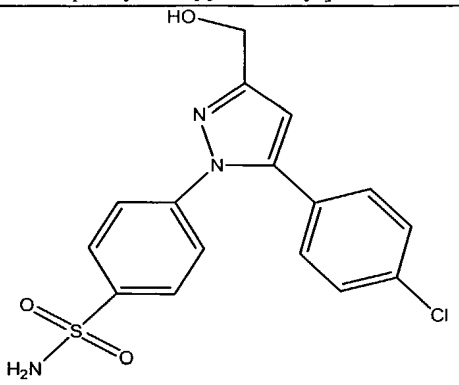
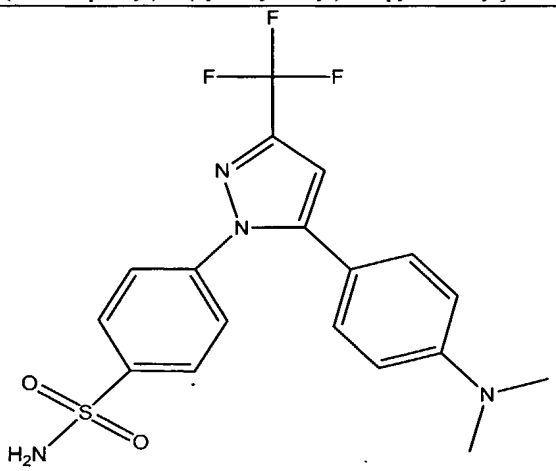
Compound Number	Structural Formula
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

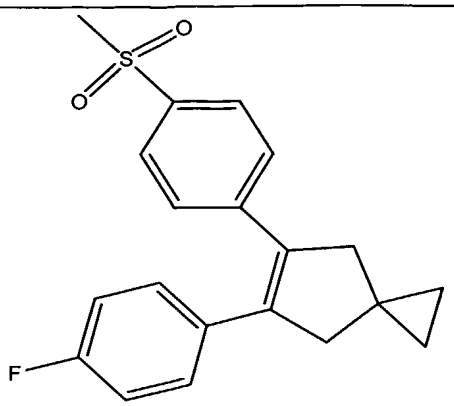
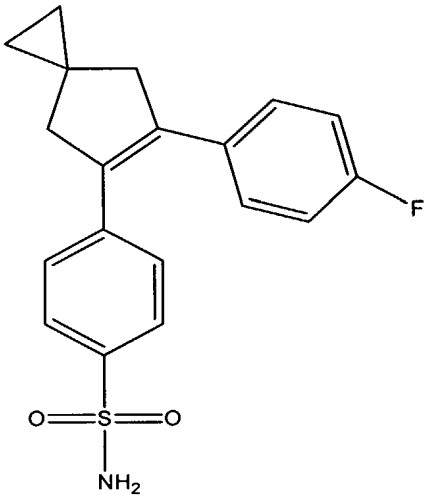
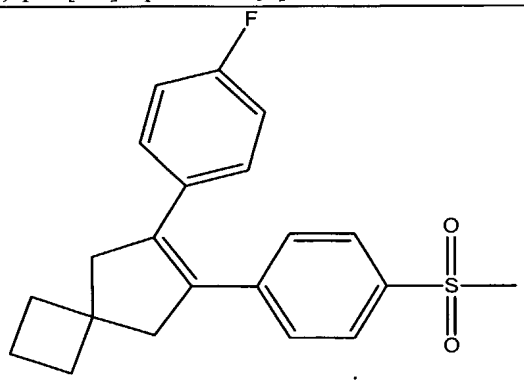
Compound Number	Structural Formula
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

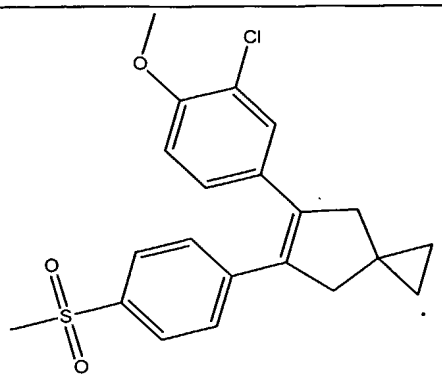
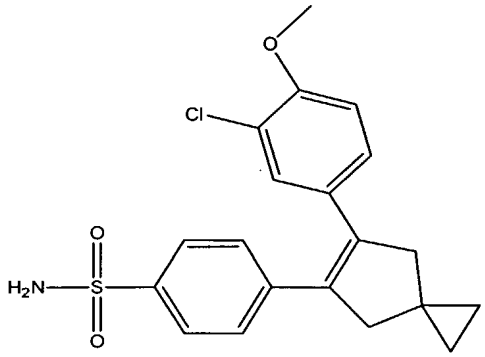
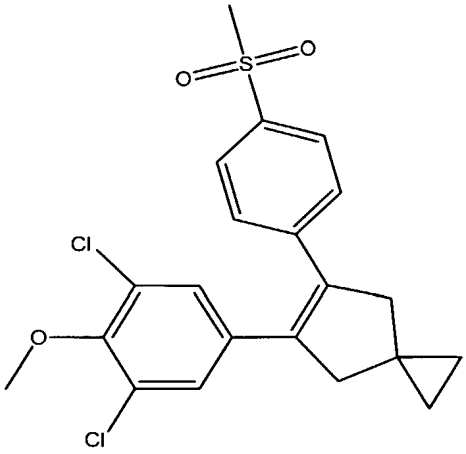
Compound Number	Structural Formula
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

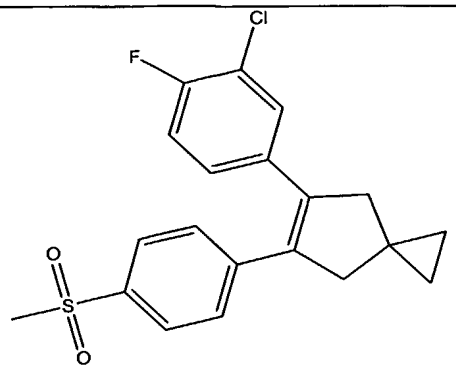
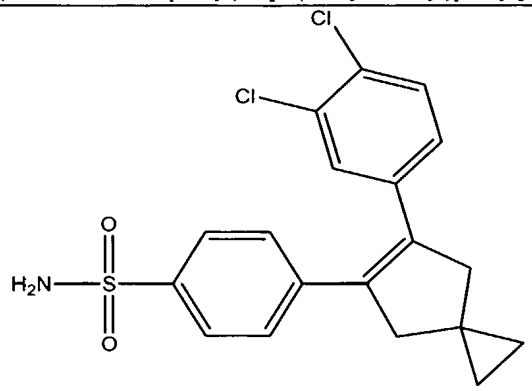
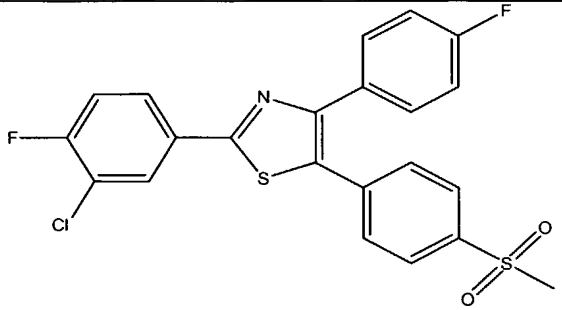
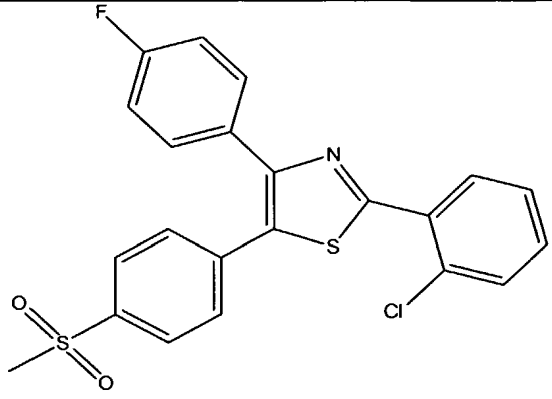
Compound Number	Structural Formula
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

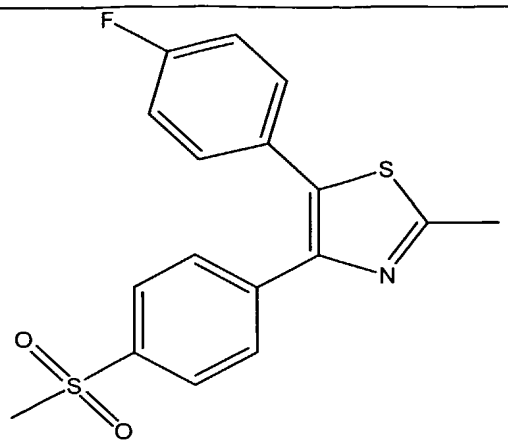
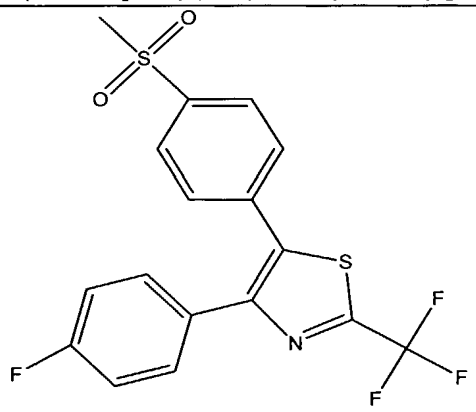
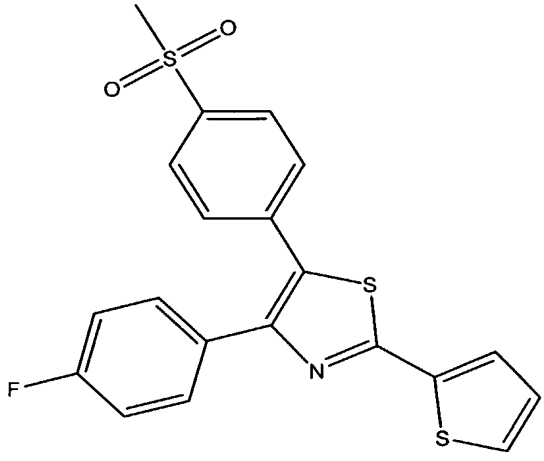
Compound Number	Structural Formula
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl] benzenesulfonamide;
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;

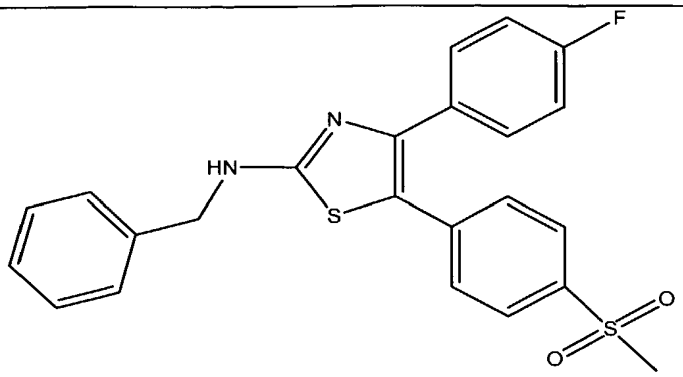
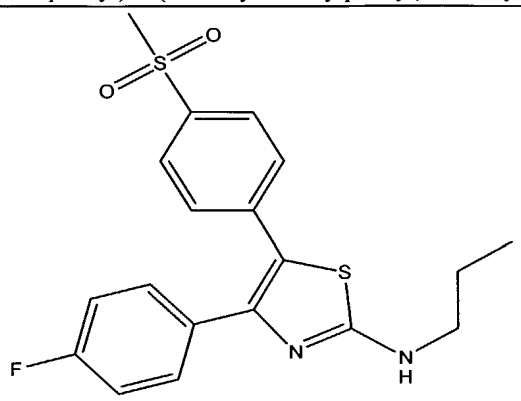
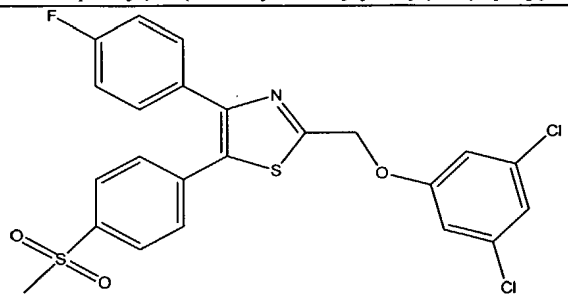
Compound Number	Structural Formula
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;

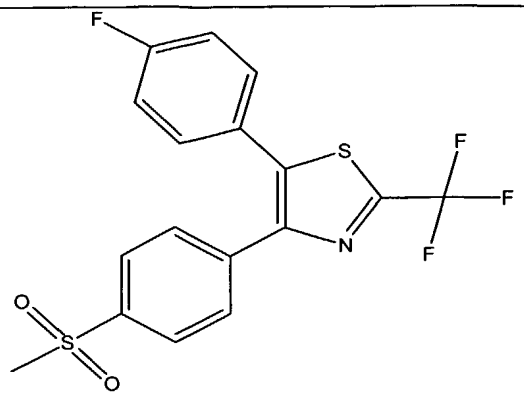
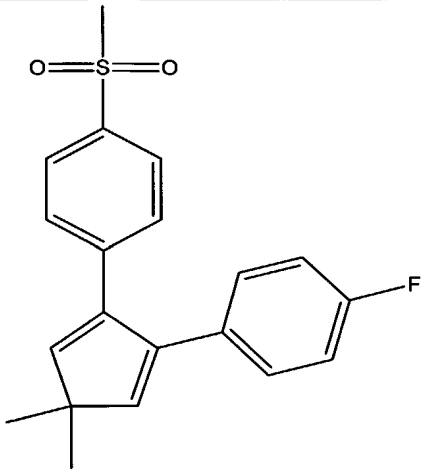
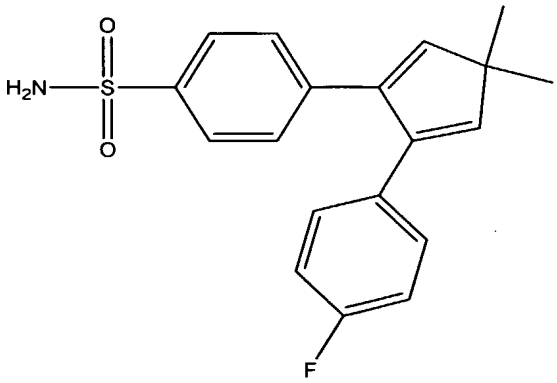
Compound Number	Structural Formula
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-105	 6-(4-fluorophenyl)-7-[4-methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

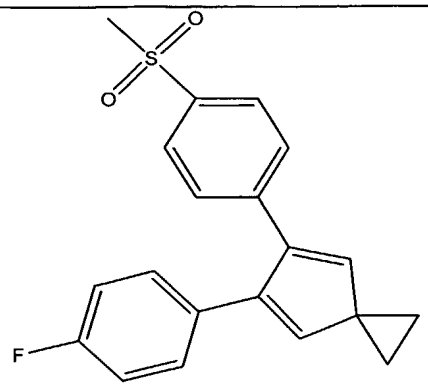
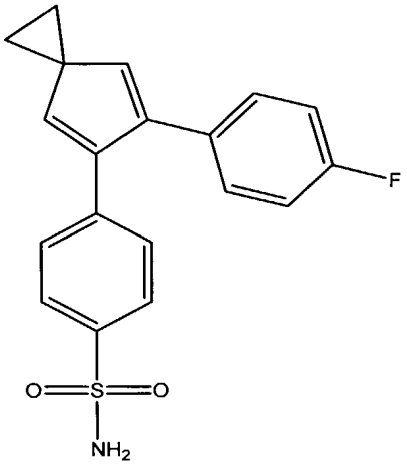
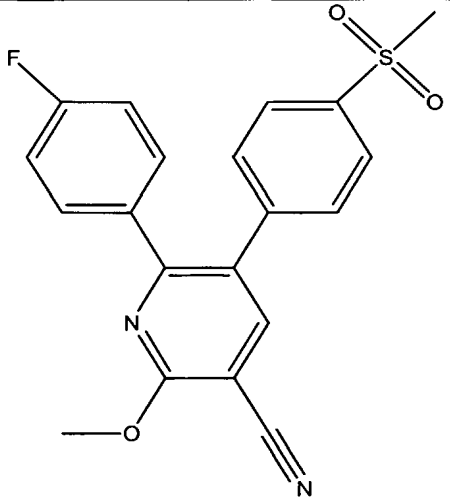
Compound Number	Structural Formula
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl] spiro[2.4]hept-5-ene;

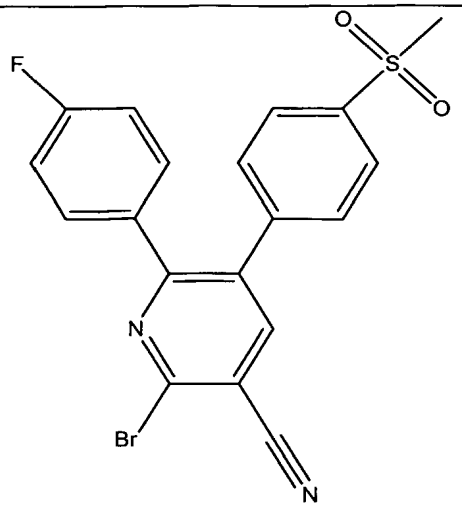
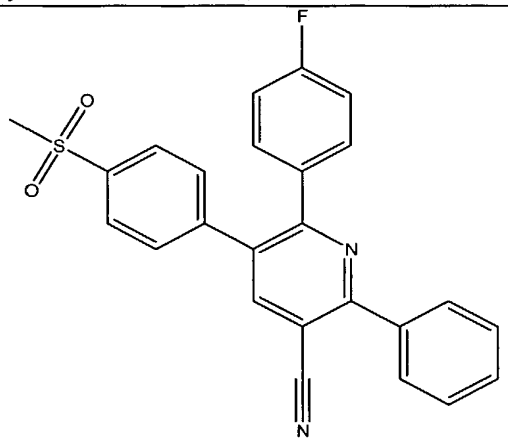
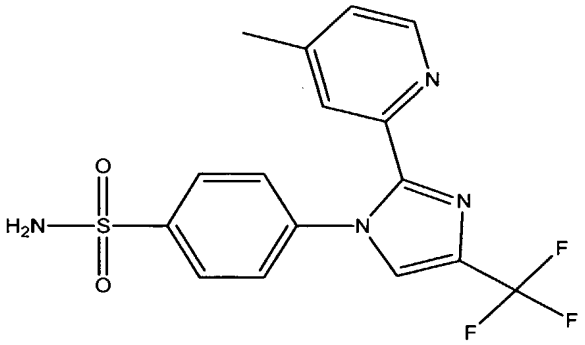
Compound Number	Structural Formula
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

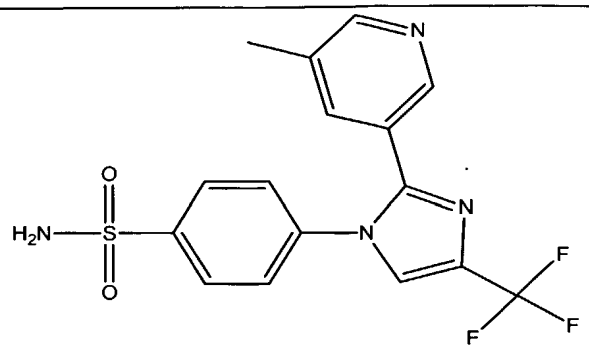
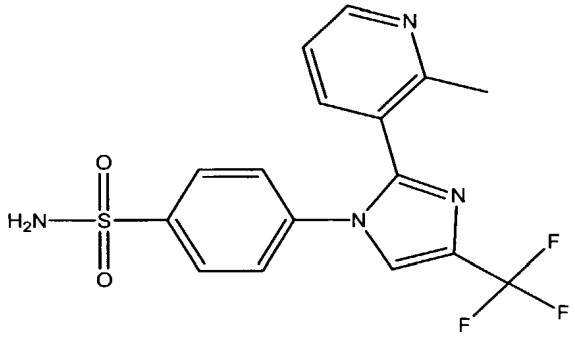
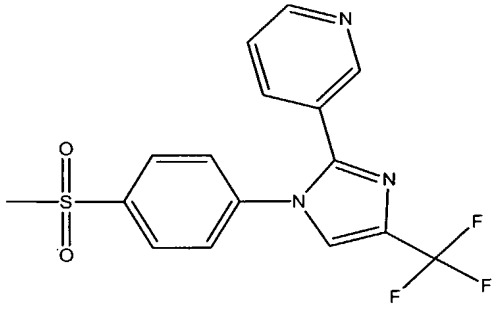
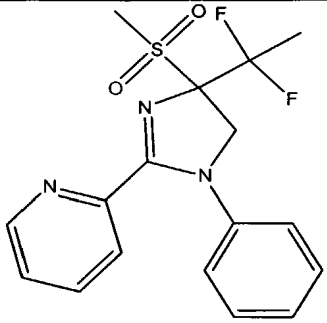
Compound Number	Structural Formula
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

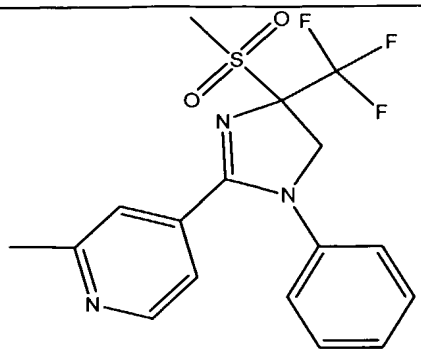
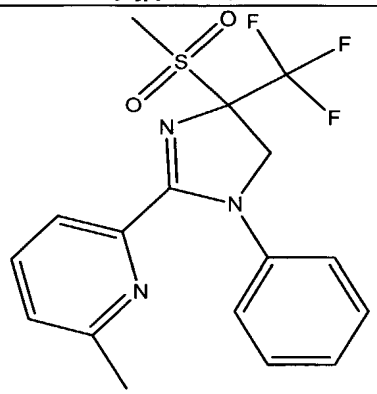
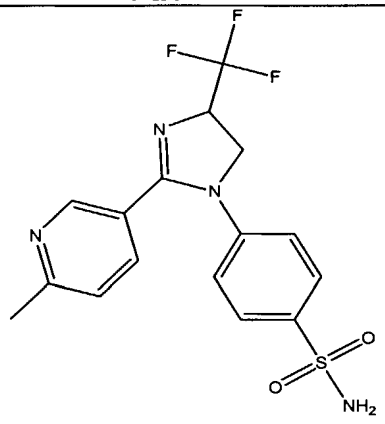
Compound Number	Structural Formula
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

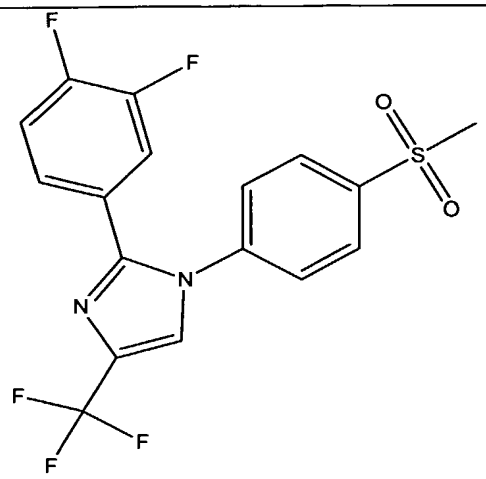
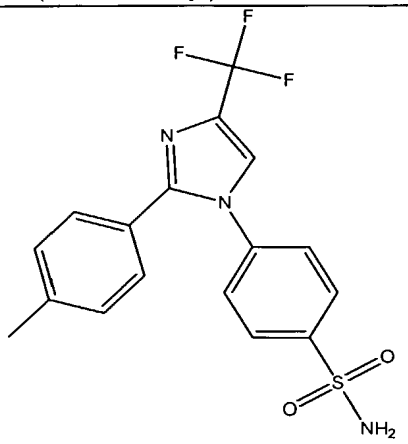
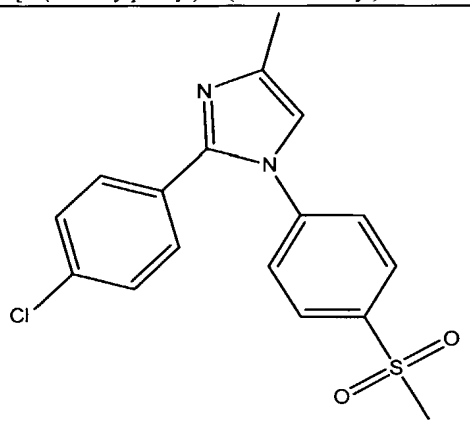
Compound Number	Structural Formula
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl) cyclopenta-2,4-dien-3-yl]benzene;
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl] benzenesulfonamide;

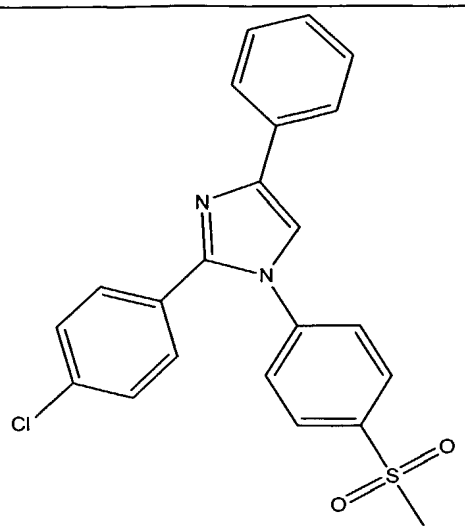
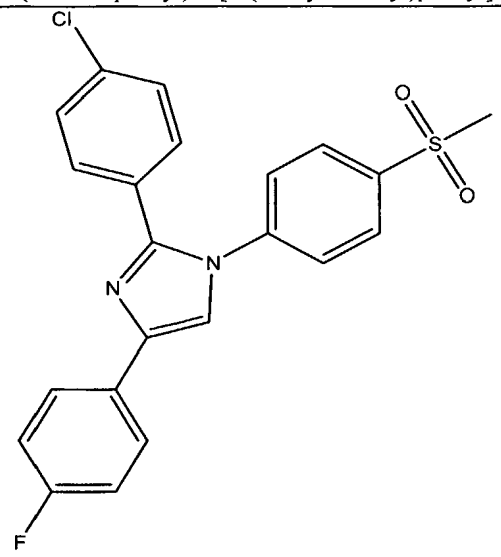
Compound Number	Structural Formula
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;

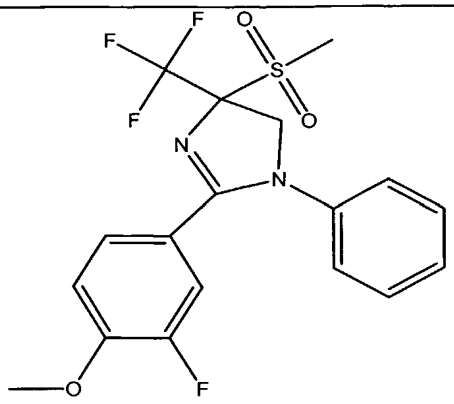
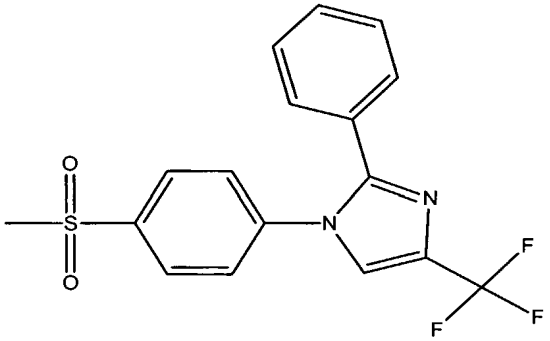
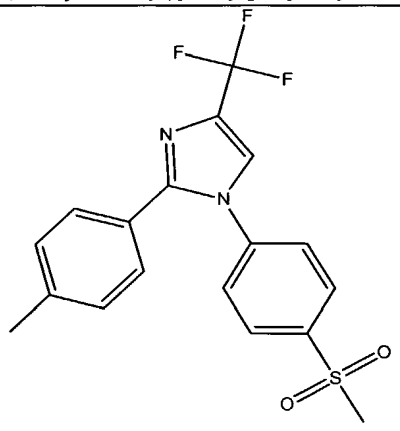
Compound Number	Structural Formula
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] -pyridine-3-carbonitrile;
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;

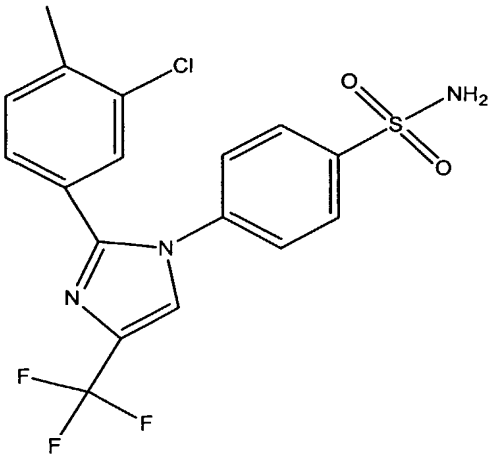
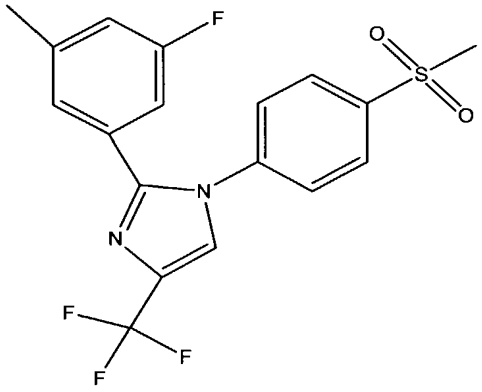
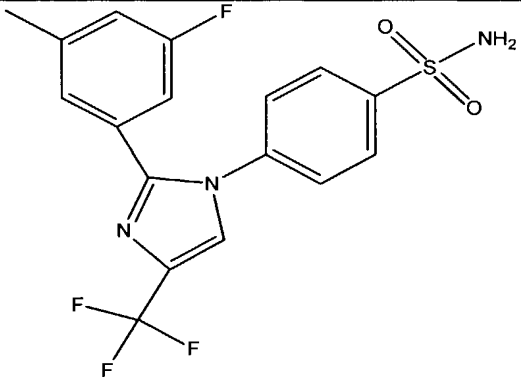
Compound Number	Structural Formula
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl] benzenesulfonamide;
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;

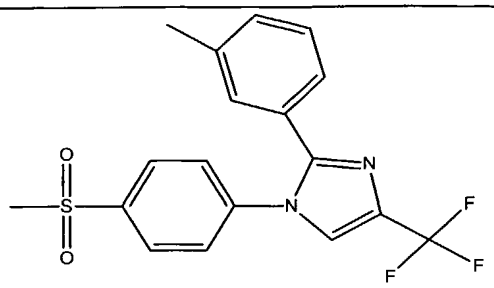
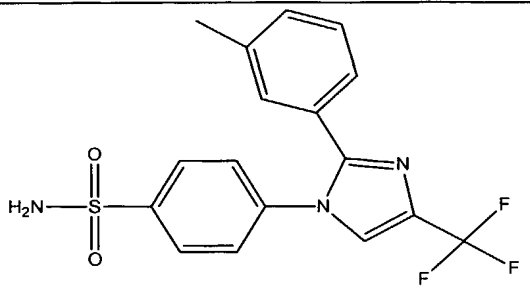
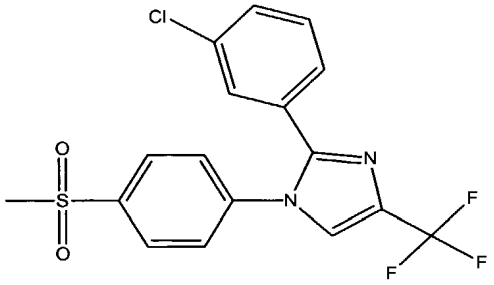
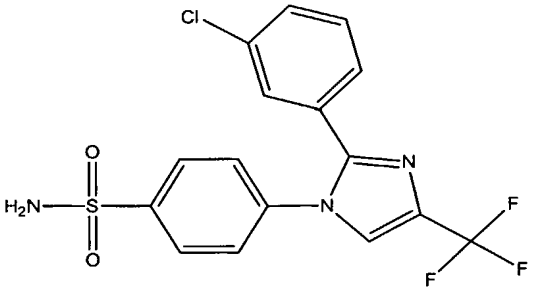
Compound Number	Structural Formula
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)] -1H-imidazol-2-yl]pyridine;
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

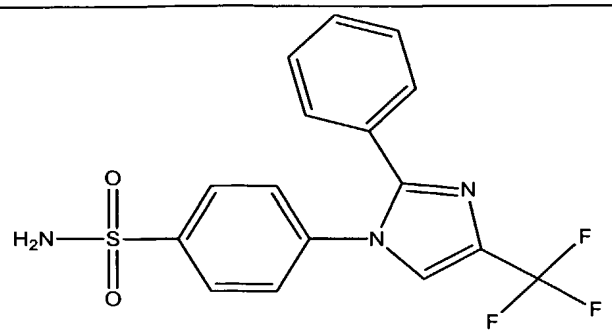
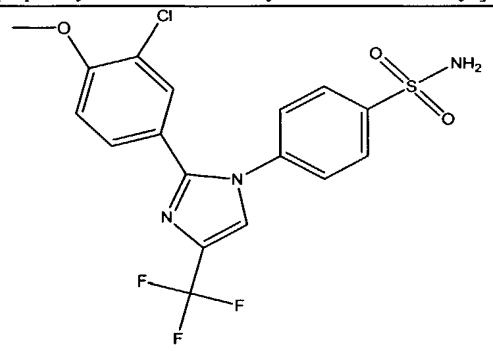
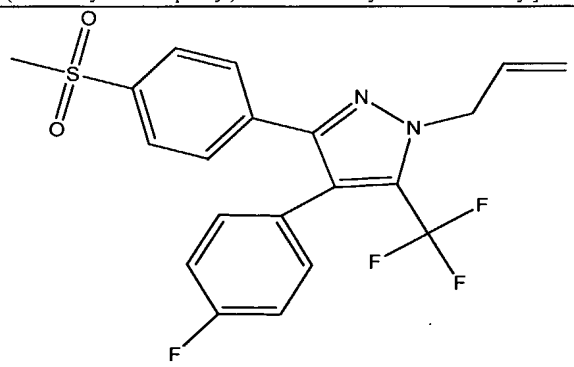
Compound Number	Structural Formula
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

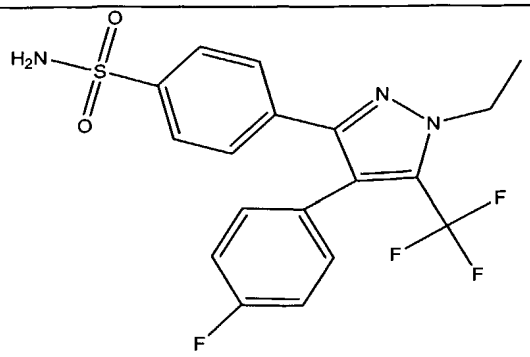
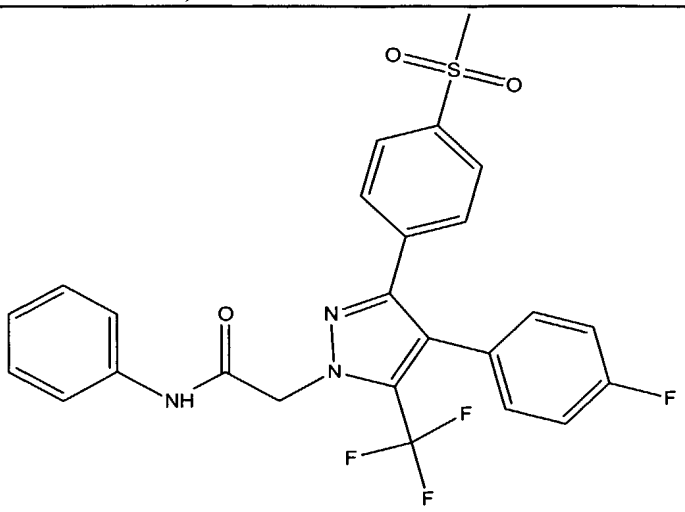
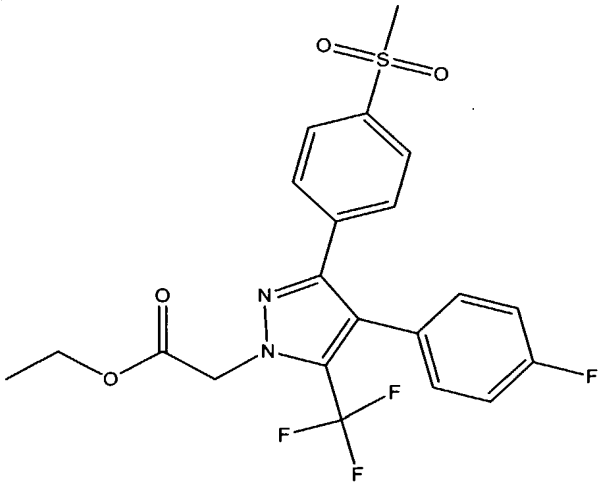
Compound Number	Structural Formula
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl] -1H-imidazole;

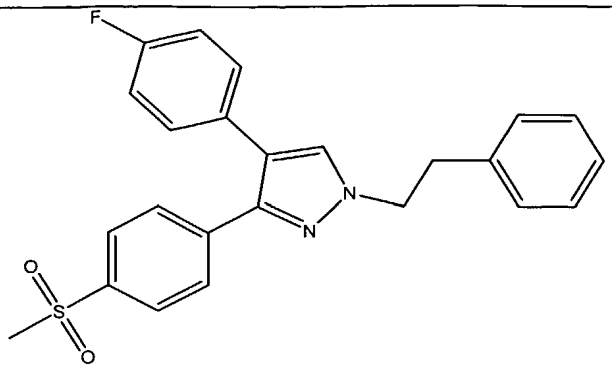
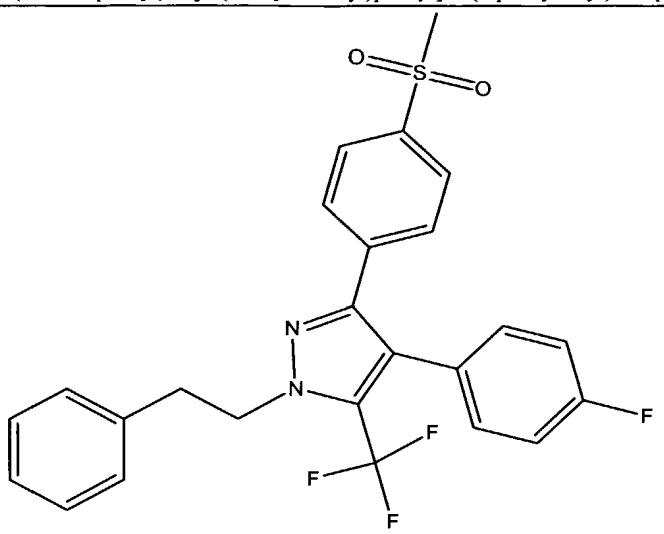
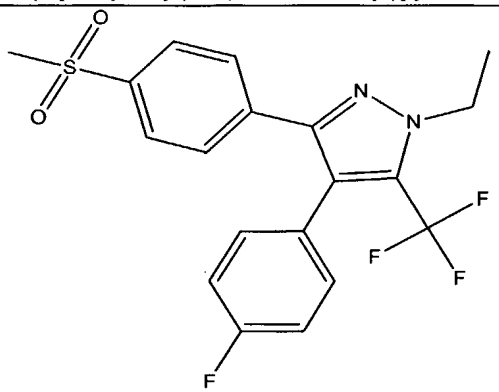
Compound Number	Structural Formula
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl -4-(trifluoromethyl)]-1H-imidazole;
B-141	 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

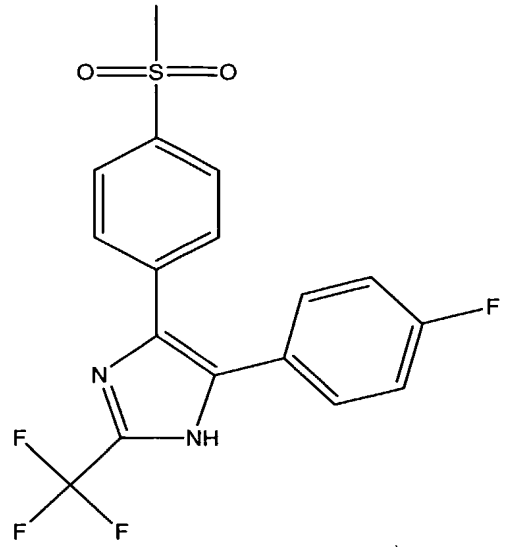
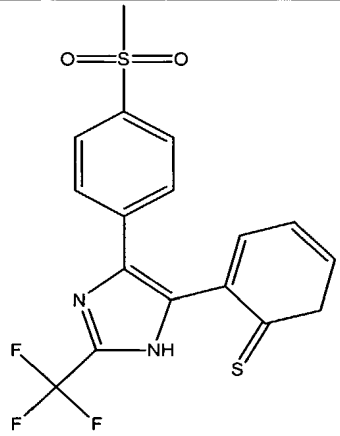
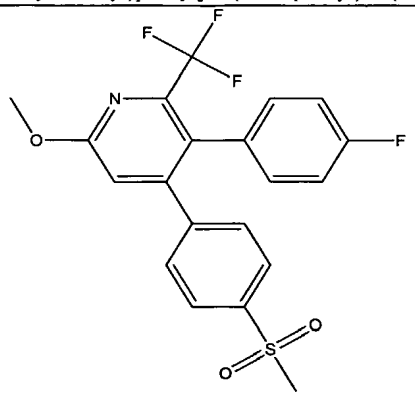
Compound Number	Structural Formula
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl] -4-(trifluoromethyl)-1H-imidazole;
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl -1H-imidazole-1-yl]benzenesulfonamide;

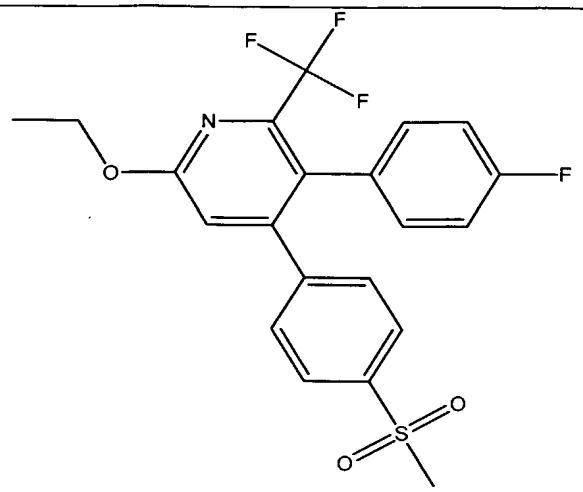
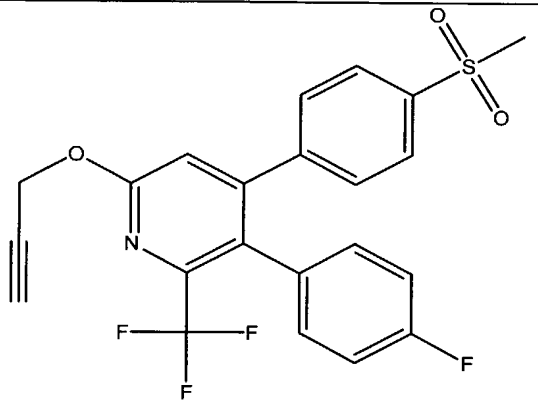
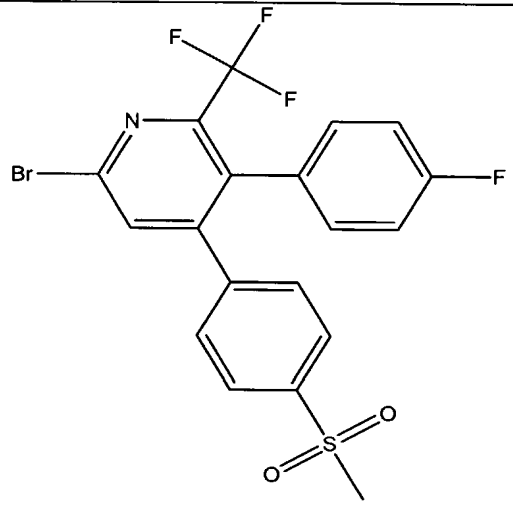
Compound Number	Structural Formula
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

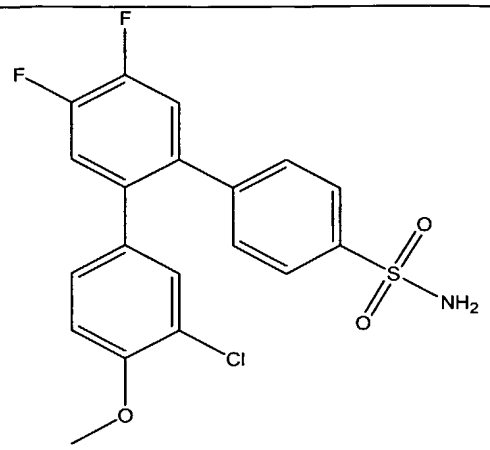
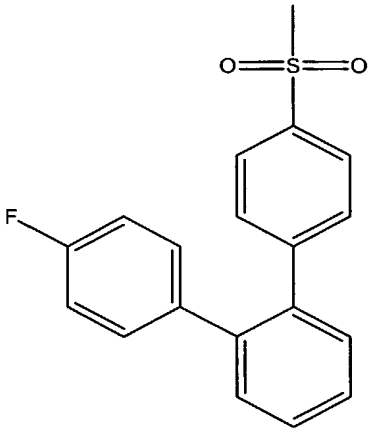
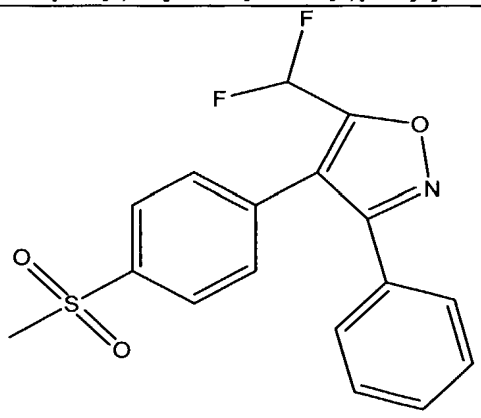
Compound Number	Structural Formula
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

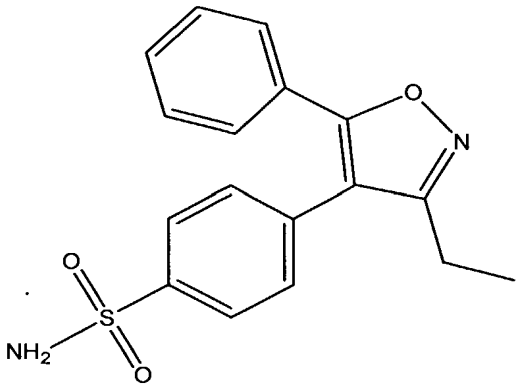
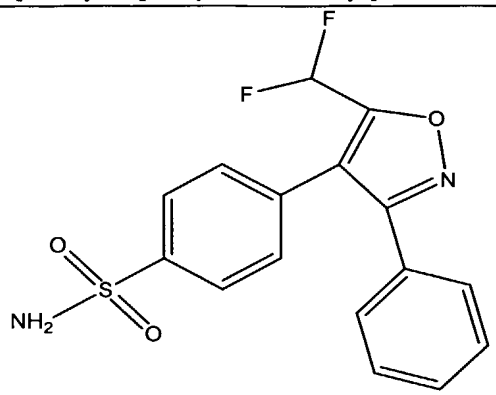
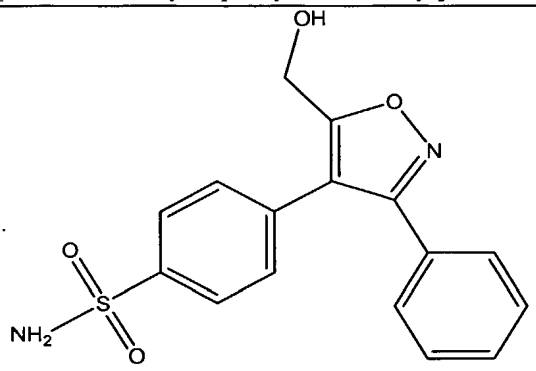
Compound Number	Structural Formula
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl] benzenesulfonamide;
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
B-155	 ethyl[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

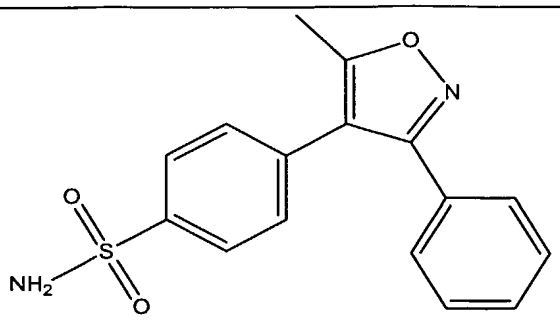
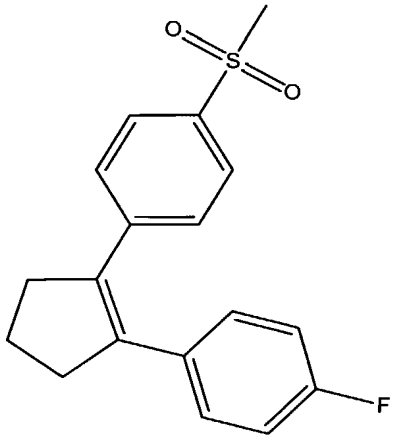
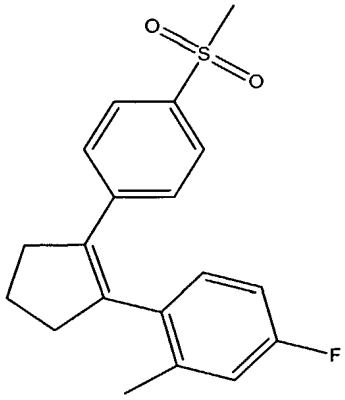
Compound Number	Structural Formula
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl] -1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-methylsulfonyl)phenyl] -5-(trifluoromethyl)-1H-pyrazole;

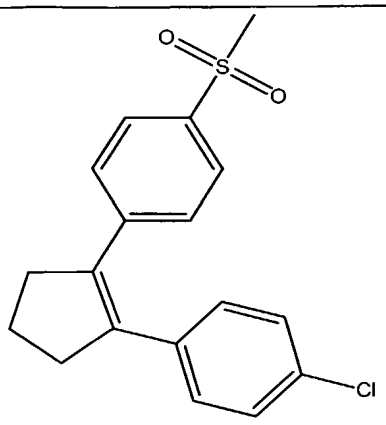
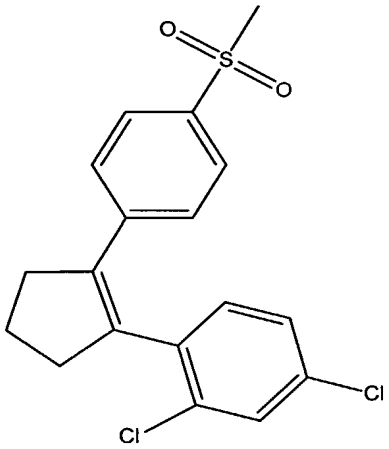
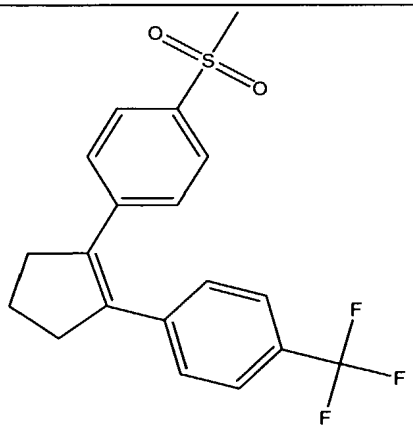
Compound Number	Structural Formula
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl) -2-trifluoromethyl-1H-imidazole;
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

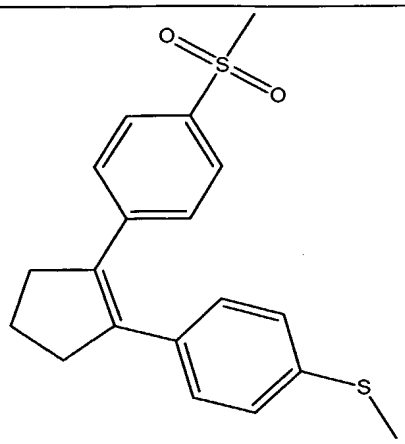
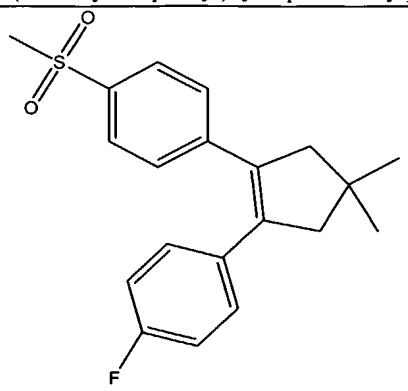
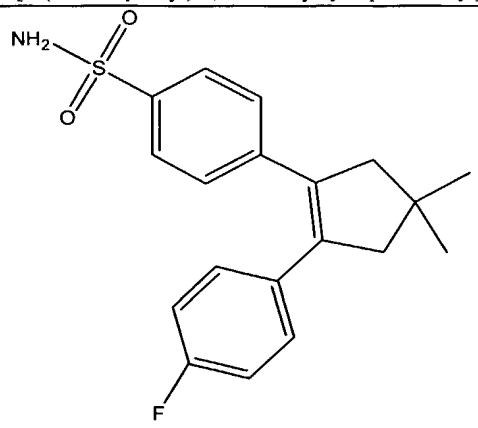
Compound Number	Structural Formula
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl] -6-(trifluoromethyl)pyridine;

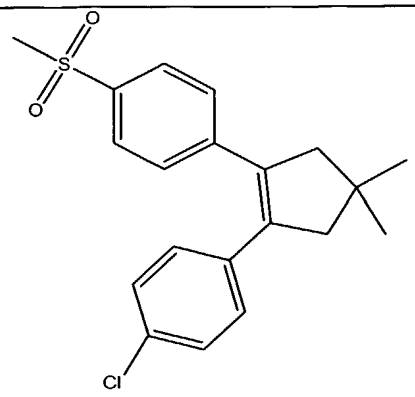
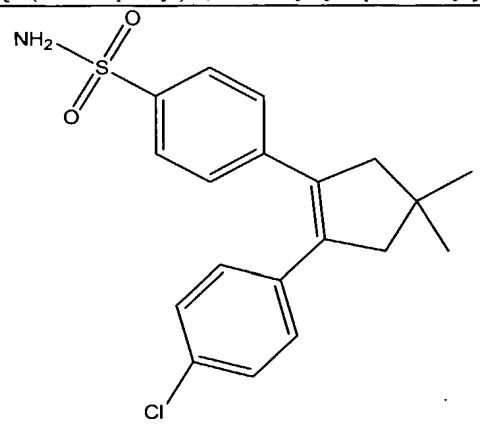
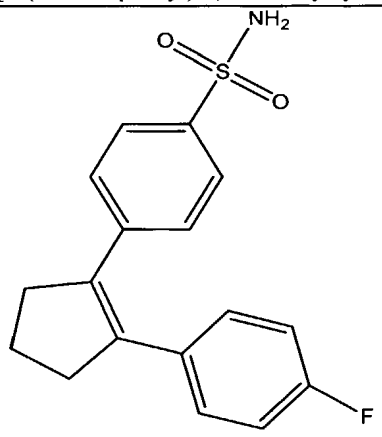
Compound Number	Structural Formula
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
B-166	 1-(4-fluorophenyl)-2-[4-methylsulfonyl)phenyl]benzene;
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

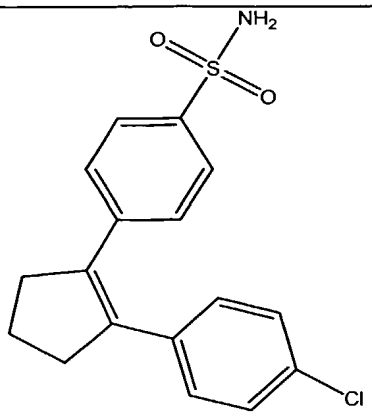
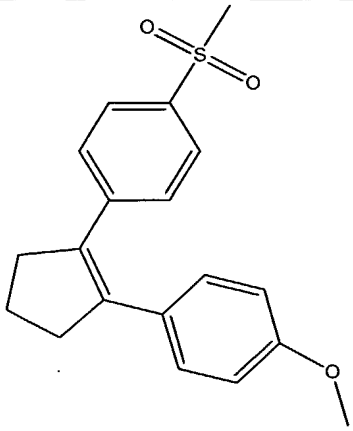
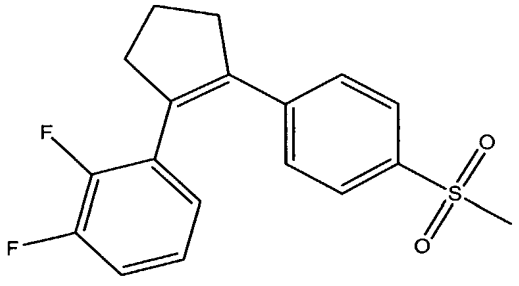
Compound Number	Structural Formula
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

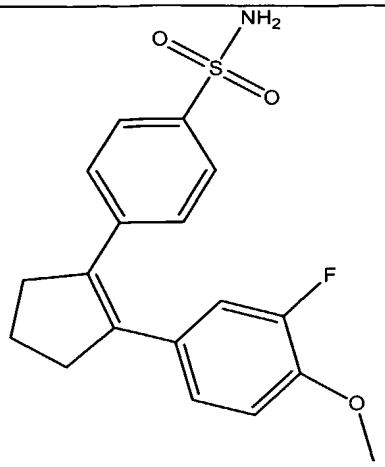
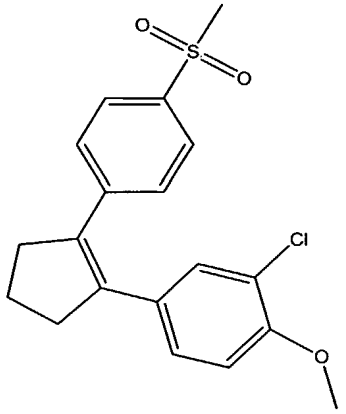
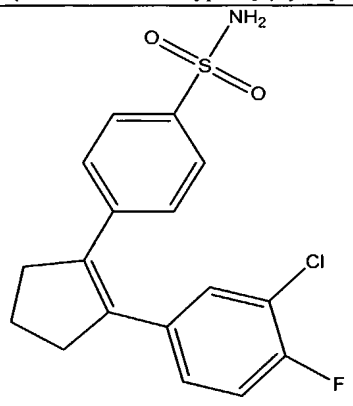
Compound Number	Structural Formula
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

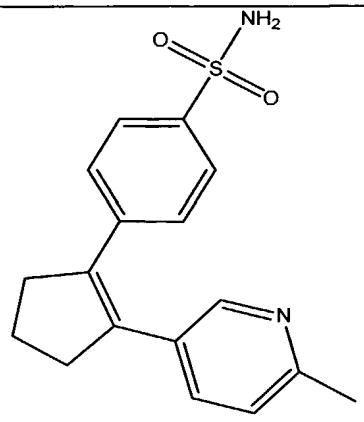
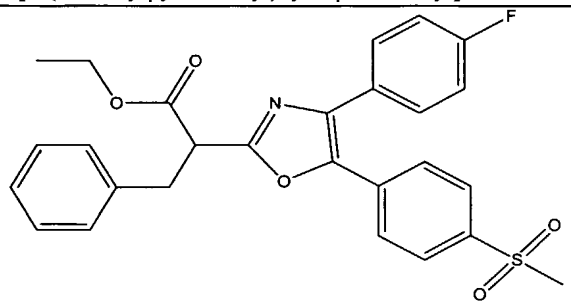
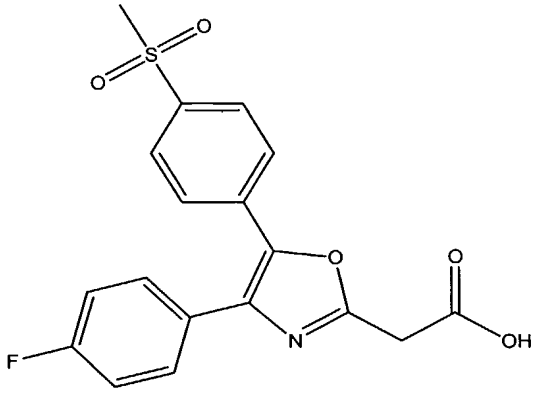
Compound Number	Structural Formula
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-176	 1-[2-(4-trifloromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

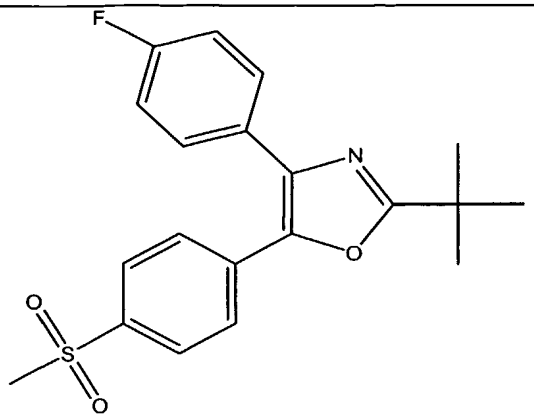
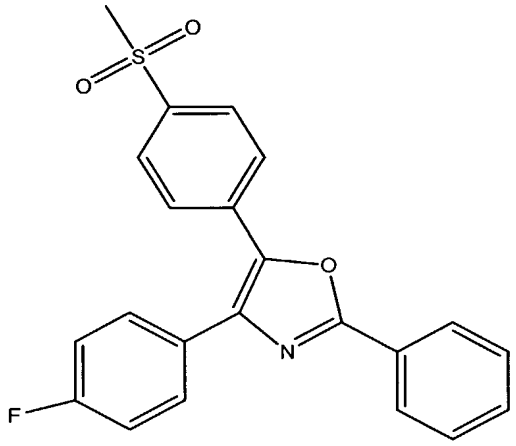
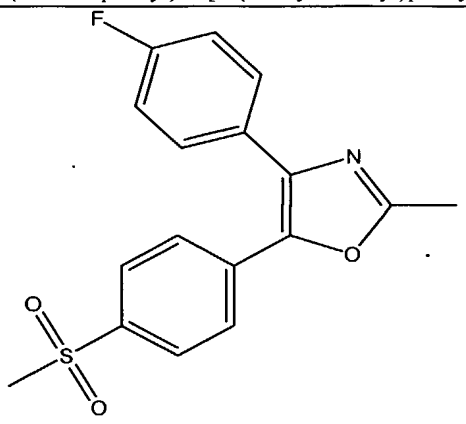
Compound Number	Structural Formula
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

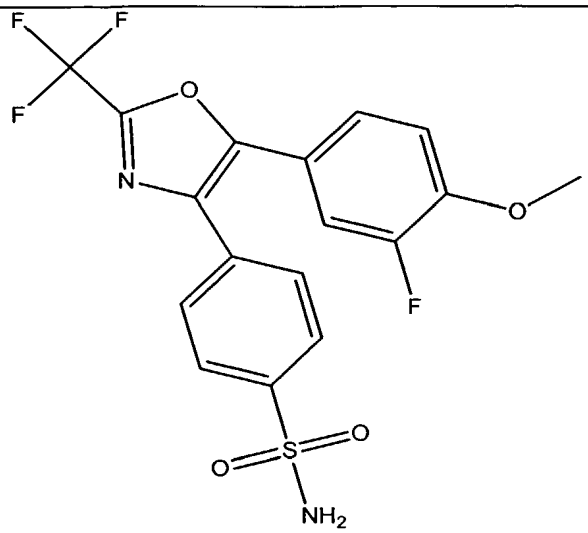
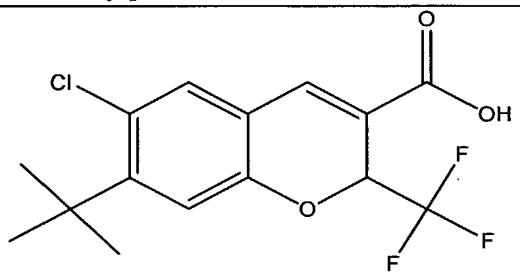
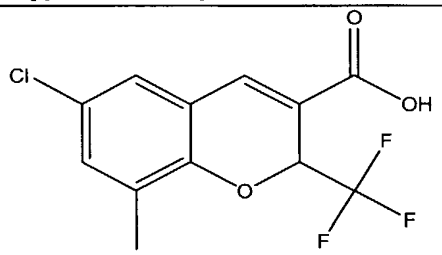
Compound Number	Structural Formula
B-180	 1-[2-(3-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

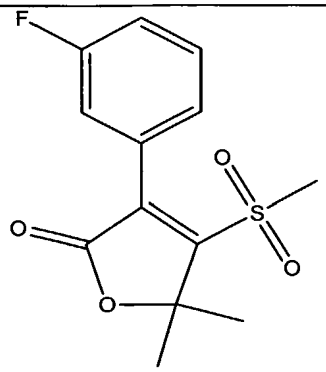
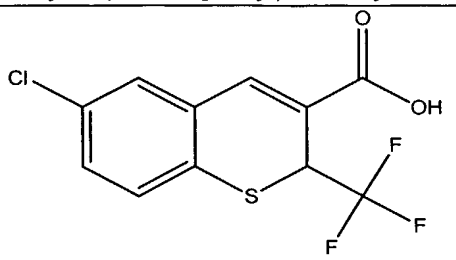
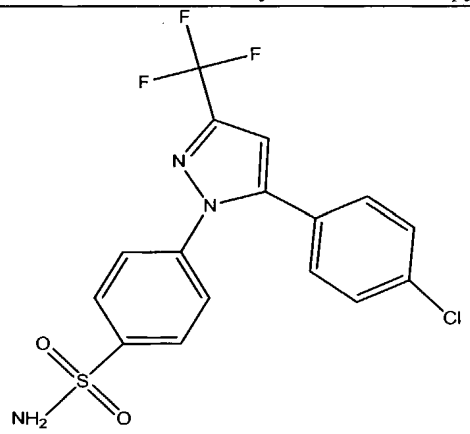
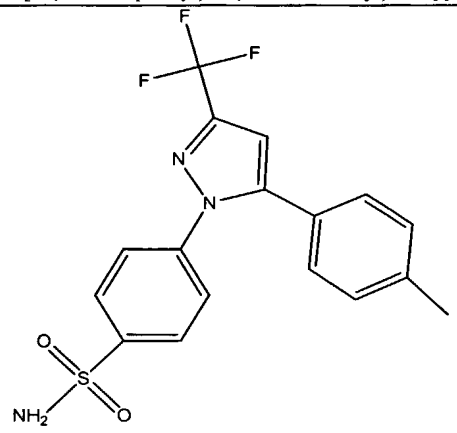
Compound Number	Structural Formula
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

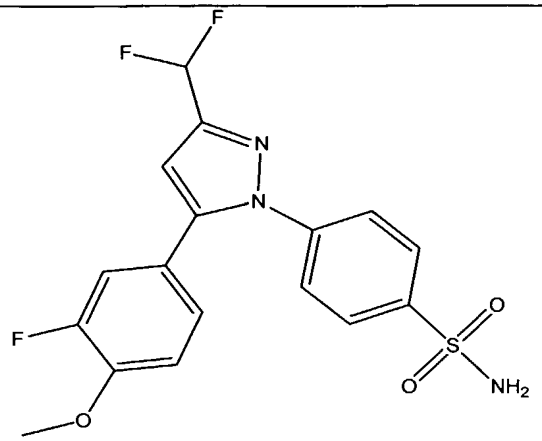
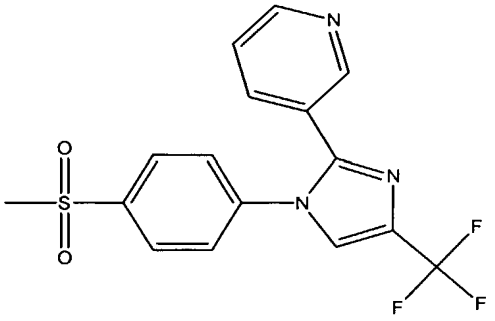
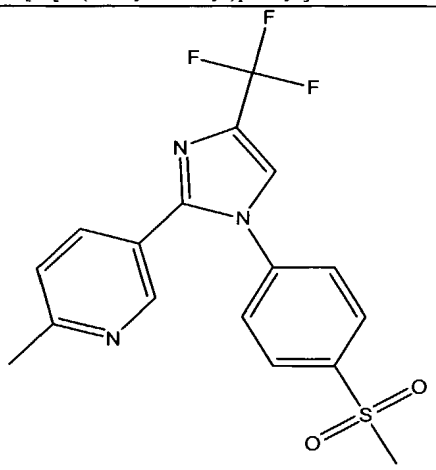
Compound Number	Structural Formula
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

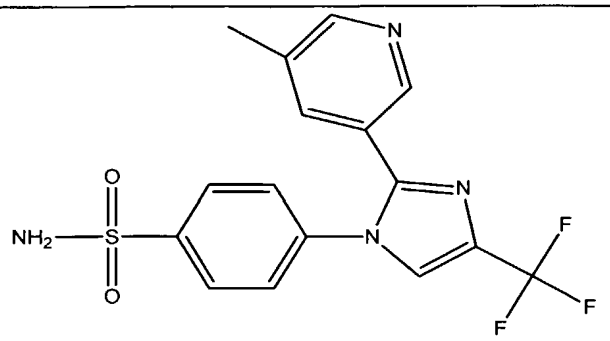
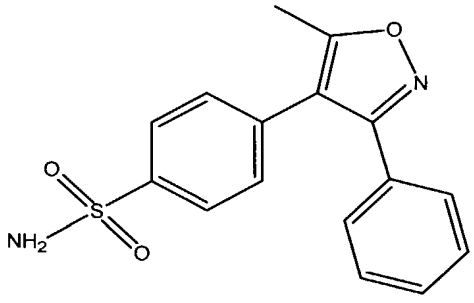
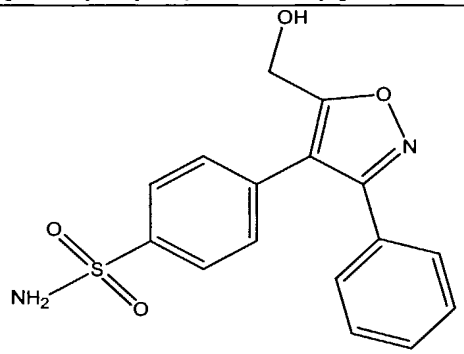
Compound Number	Structural Formula
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

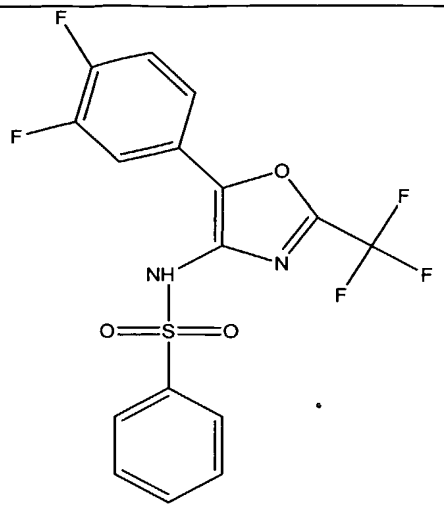
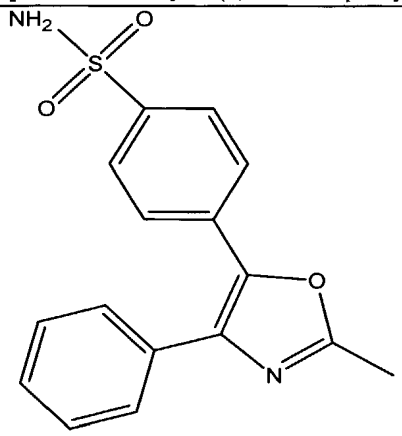
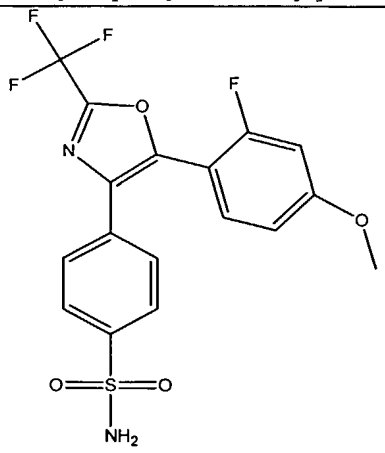
Compound Number	Structural Formula
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;

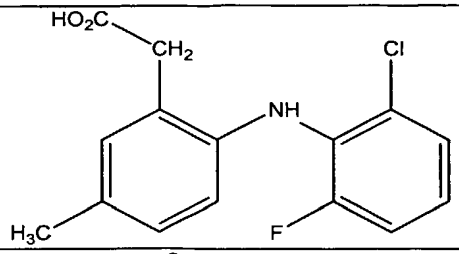
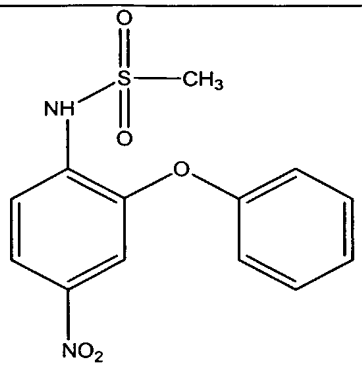
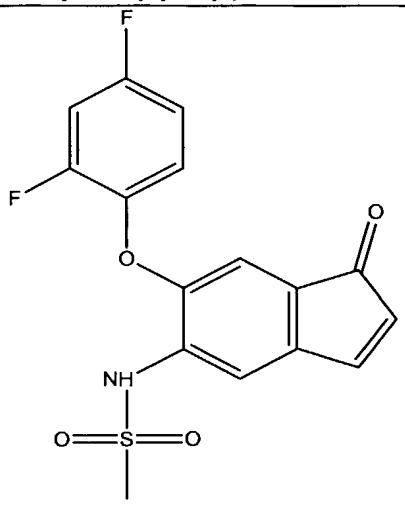
Compound Number	Structural Formula
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl -4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H -1-benzopyran-3-carboxylic acid;
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

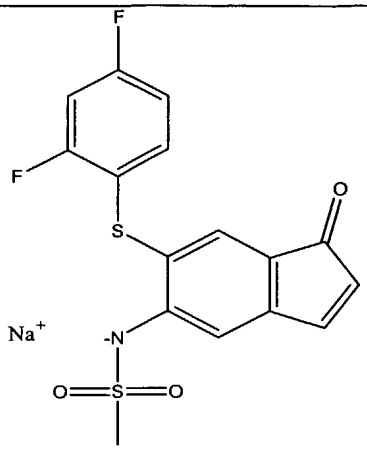
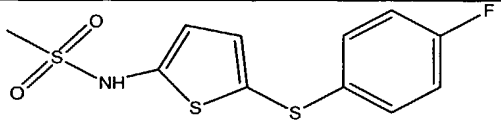
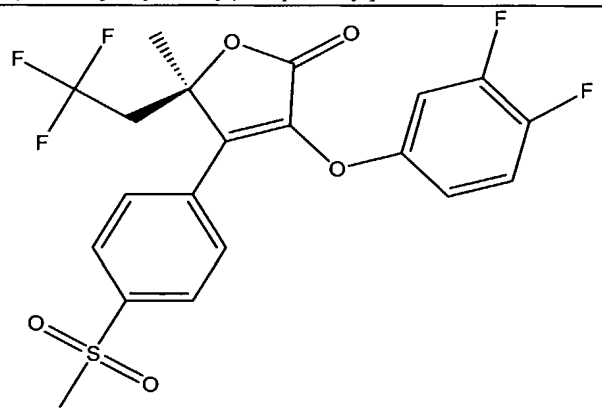
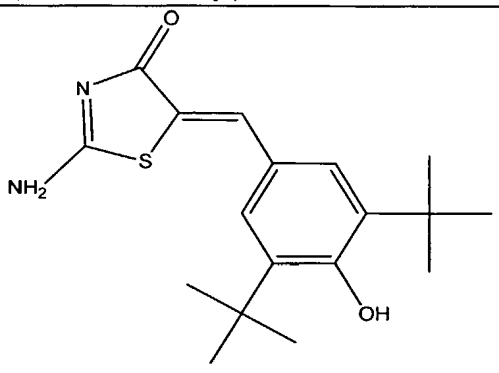
Compound Number	Structural Formula
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

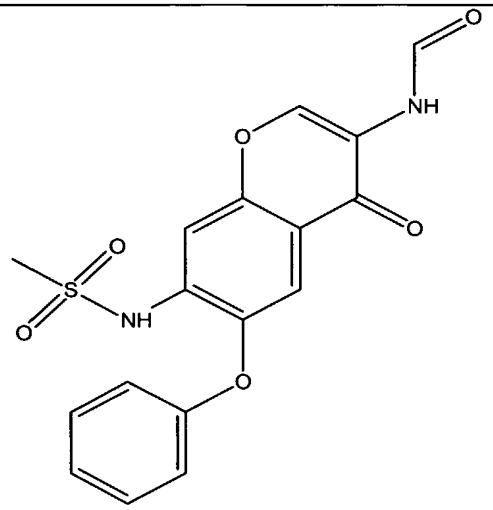
Compound Number	Structural Formula
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl) -1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl -1H-imidazol-2-yl]pyridine;

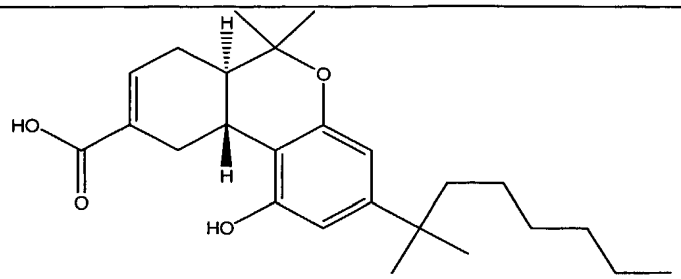
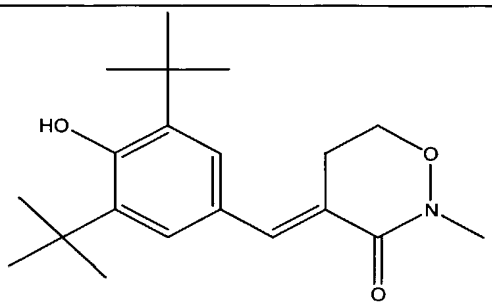
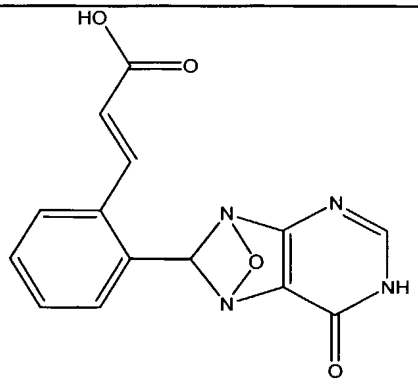
Compound Number	Structural Formula
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl) -1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

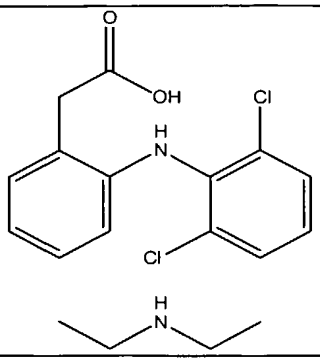
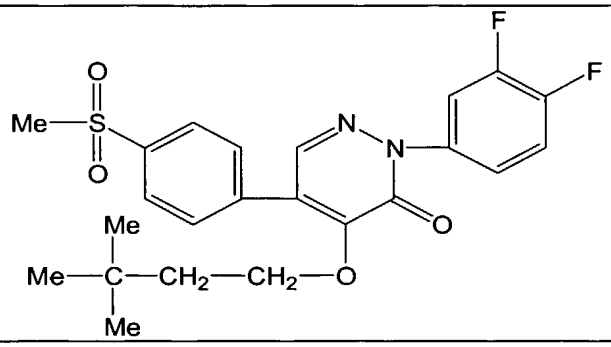
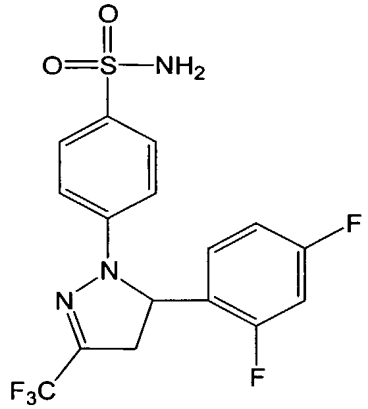
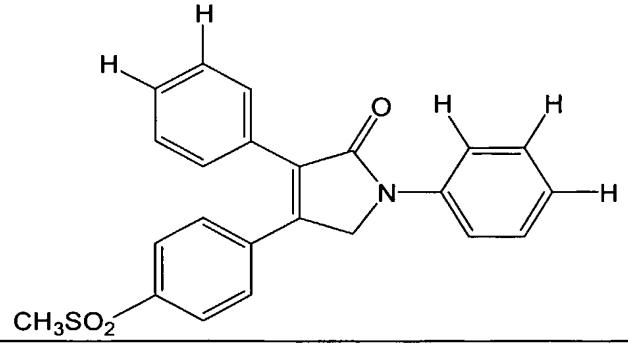
Compound Number	Structural Formula
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

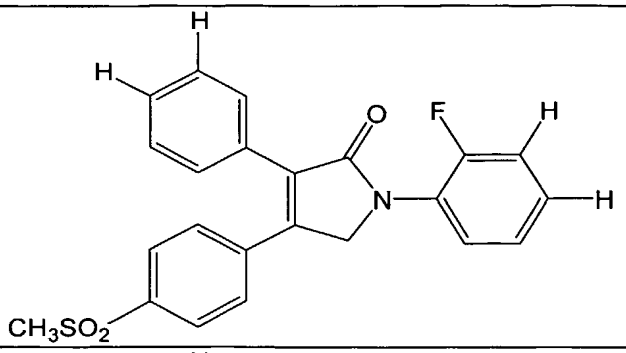
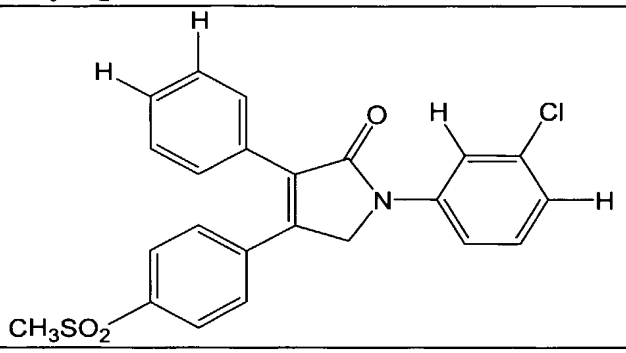
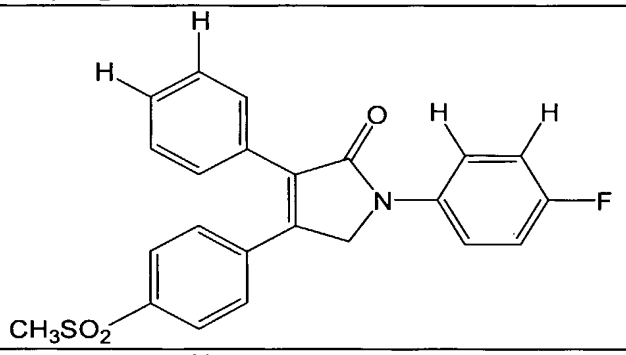
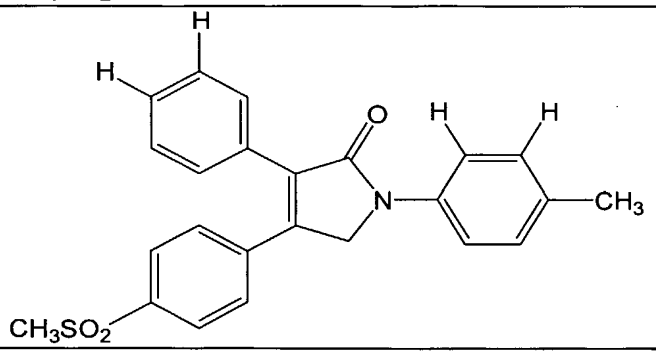
Compound Number	Structural Formula
B-211	
B-212	 *N*-(4-nitro-2-phenoxy-phenyl)-methanesulfonamide
B-213	 N-[6-(2,4-difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide

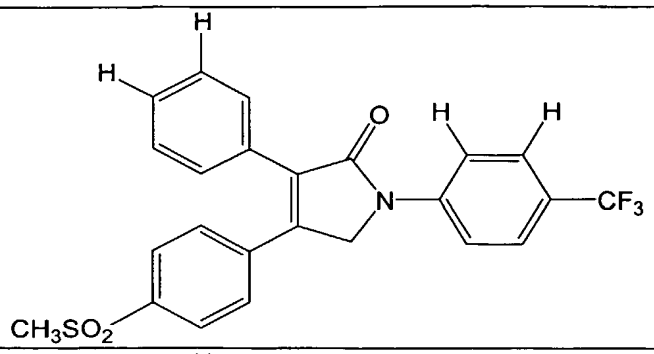
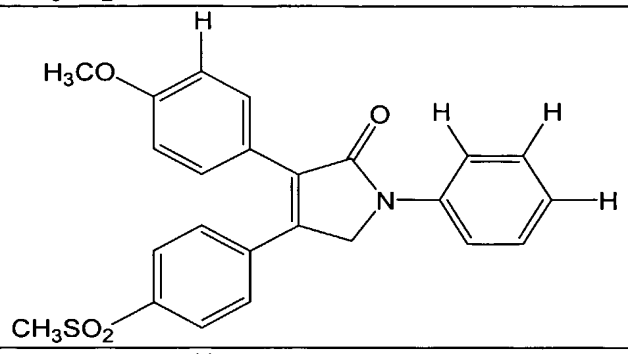
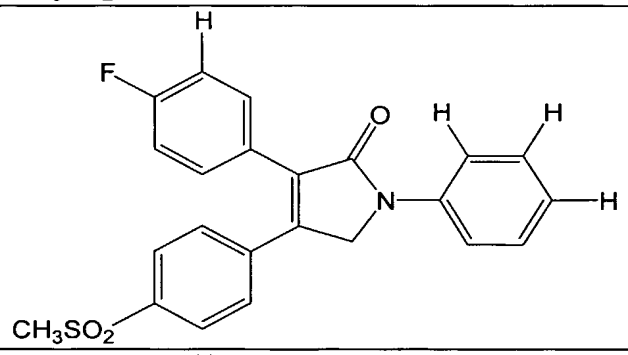
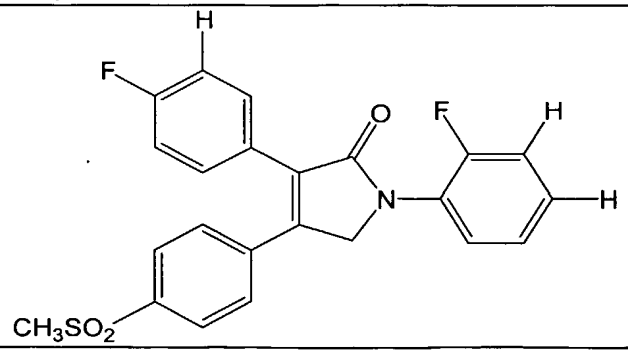
Compound Number	Structural Formula
B-214	 *N*-[6-(2,4-difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide
B-216	 3-(3,4-difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] -4(5H)-thiazolone

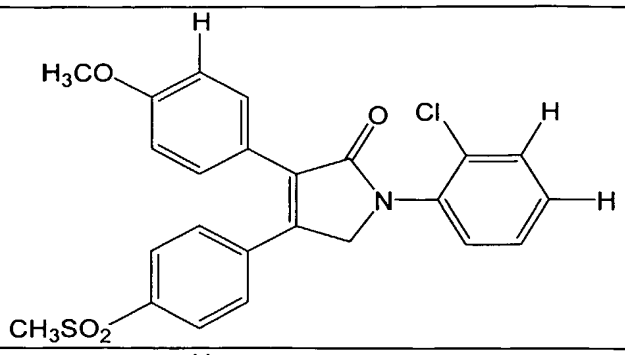
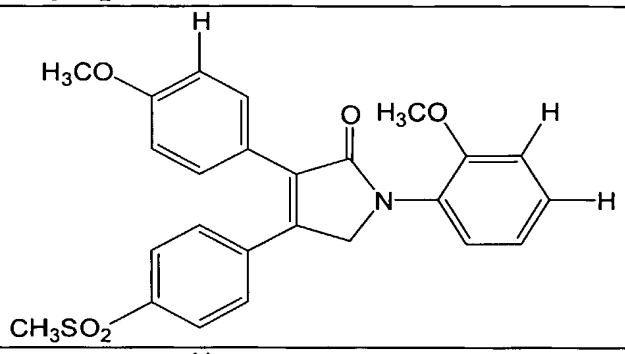
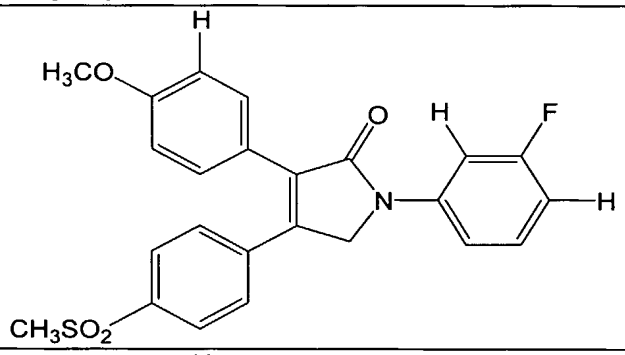
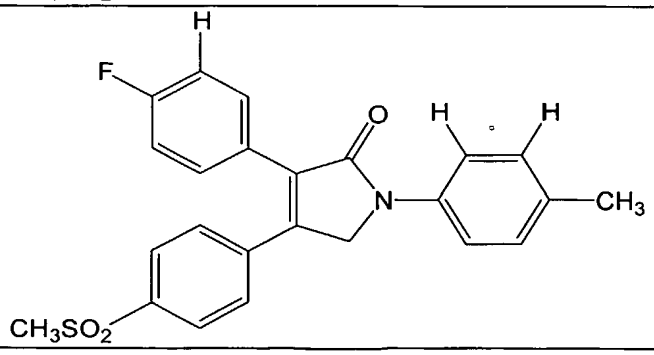
Compound Number	Structural Formula
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl] -methanesulfonamide
B-225	D-1367
B-226	L-748731

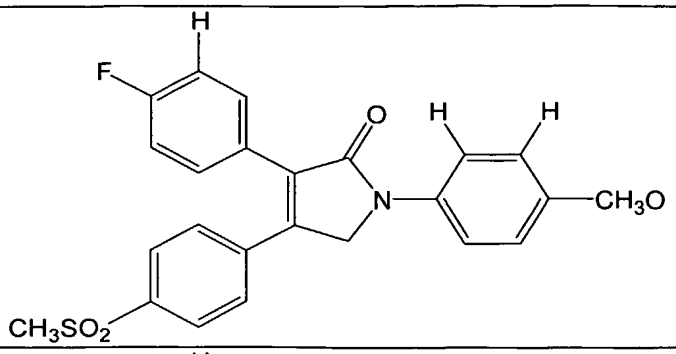
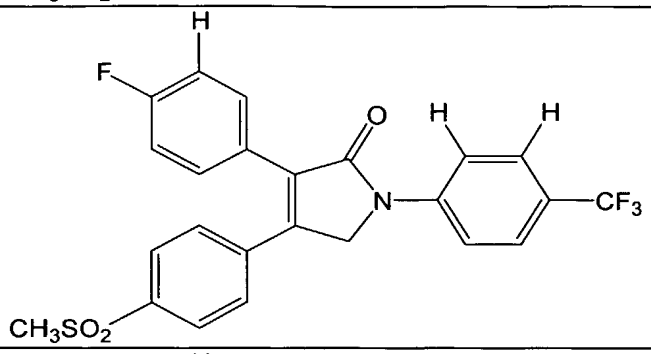
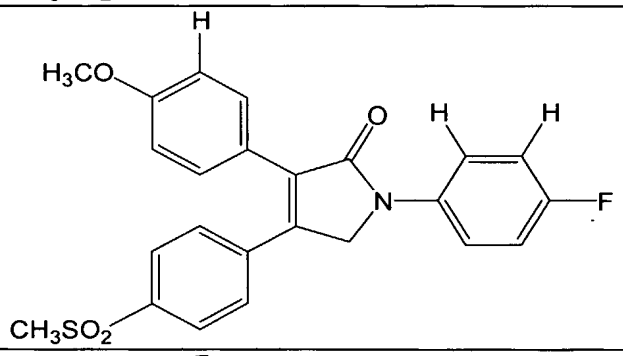
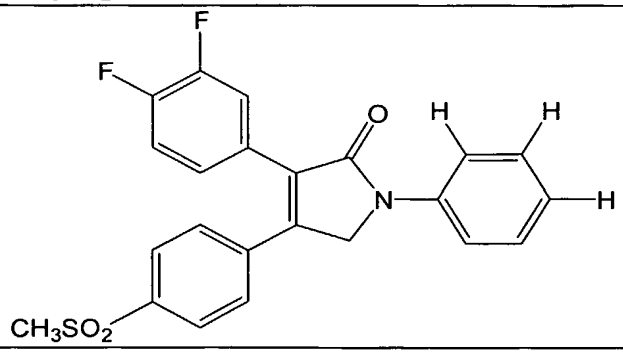
Compound Number	Structural Formula
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid
B-228	CGP-28238
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene] dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474

Compound Number	Structural Formula
B-233	
B-234	
B-235	
B-236	

Compound Number	Structural Formula
B-237	
B-238	
B-239	
B-240	

Compound Number	Structural Formula
B-241	
B-242	
B-243	
B-244	

Compound Number	Structural Formula
B-245	
B-246	
B-247	
B-248	

Compound Number	Structural Formula
B-249	
B-250	
B-251	
B-252	

[0415] The cyclooxygenase-2 selective inhibitor employed in the present invention can exist in tautomeric, geometric or stereoisomeric forms. Generally speaking, suitable cyclooxygenase-2 selective inhibitors that are in tautomeric, geometric or stereoisomeric forms are those compounds that inhibit cyclooxygenase-2 activity by about 25%, more typically by about 50%, and even more typically, by about

75% or more when present at a concentration of 100 μM or less. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the invention. The terms "cis" and "trans", as used herein, denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms. Furthermore, some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures or R and S forms for each stereocenter present.

[0416] The cyclooxygenase-2 selective inhibitors utilized in the present invention may be in the form of free bases or pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically-acceptable salts" are salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt may vary, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds for use in the present methods may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of use in the present methods include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for

example, the appropriate acid or base with the compound of any Formula set forth herein.

[0417] The cyclooxygenase-2 selective inhibitors of the present invention can be formulated into pharmaceutical compositions and administered by a number of different means that will deliver a therapeutically effective dose. Such compositions can be administered orally, parenterally, by inhalation spray, rectally, intradermally, transdermally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania (1975), and Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y. (1980).

[0418] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are useful in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, and polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

[0419] Suppositories for rectal administration of the compounds discussed herein can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0420] Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds are

ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds can be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

[0421] For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0422] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[0423] The amount of active ingredient that can be combined with the carrier materials to produce a single dosage of the cyclooxygenase-2 selective inhibitor will vary depending upon the patient and the particular mode of administration. In general, the pharmaceutical compositions may contain a cyclooxygenase-2 selective inhibitor in the range of about 0.1 to 2000 mg, more typically, in the range of about 0.5 to 500 mg and still more typically, between about 1 and 200 mg. A daily dose of about 0.01 to 100 mg/kg body weight, or more typically, between about 0.1 and about 50 mg/kg body weight and even more typically, from about 1 to 20 mg/kg body weight, may be

appropriate. The daily dose is generally administered in one to about four doses per day.

[0424] In one embodiment, when the cyclooxygenase-2 selective inhibitor comprises rofecoxib, it is typical that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more typically, from about 0.18 to about 0.4 mg/day·kg.

[0425] In still another embodiment, when the cyclooxygenase-2 selective inhibitor comprises etoricoxib, it is typical that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0426] Further, when the cyclooxygenase-2 selective inhibitor comprises celecoxib, it is typical that the amount used is within a range of from about 1 to about 20 mg/day·kg, even more typically, from about 1.4 to about 8.6 mg/day·kg, and yet more typically, from about 2 to about 3 mg/day·kg.

[0427] When the cyclooxygenase-2 selective inhibitor comprises valdecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 0.8 to about 4 mg/day·kg.

[0428] In a further embodiment, when the cyclooxygenase-2 selective inhibitor comprises parecoxib, it is typical that the amount used is within a range of from about 0.1 to about 5 mg/day·kg, and even more typically, from about 1 to about 3 mg/day·kg.

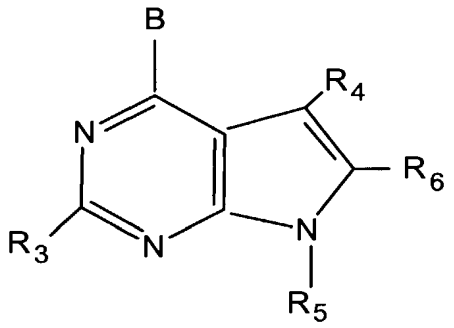
[0429] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

[0430] In addition to a cyclooxygenase-2 selective inhibitor, the combination therapy of the present invention comprises a corticotropin releasing factor antagonist. In one embodiment, the corticotropin releasing factor antagonist in this therapeutic combination is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695 (N-(2-chloro-4,6-dimethylphenyl)-1-[1-methoxymethyl-(2-

methoxyethyl]-6-methyl-1H-1,2,3-triazolo[4,5-c]pyridin-4-amine mesylate)), D-PheCRF 12-41, and N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine. In one embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41, antalarmin, CP-154,526, and astressin. In another embodiment, the corticotropin releasing factor antagonist is selected from the group consisting of *α*-helical CRF 9-41 and antalarmin. In yet another embodiment, the corticotropin releasing factor antagonist of this therapeutic combination is *α*-helical CRF 9-41.

[0431] In one embodiment, the corticotropin releasing factor antagonist is represented by Formula *(VI)*:



(VI)

[0432] wherein:

[0433] B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCR_1R_2R_{11}$, $-OCR_1R_2R_{11}$, $-SCR_1R2R_{11}$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$, $-CR_2R_{11}OR_1$, $-CR_2R_{11}SR_1$, or $-C(O)R_2$;

[0434] R_1 is hydrogen, or C_1-C_6 alkyl optionally substituted with from one to two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, $-O(C_1$-C_6 alkyl), $-ONH(C_1$-C_4 alkyl), $-ON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), amino, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl), $-S(C_1$-C_6 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NH(C_1$-C_4 alkyl), -COOH, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, $-NO_2$, $-SO(C_1$-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl), $-SO_2$ NH(C_1-C_4 alkyl), $-SO_2$ (C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_1 may contain one or two double or triple bonds;

[0435] R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl,

furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein one or two of the carbon atoms of any of said cycloalkyl moieties may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl or C_1-C_4 alkanoyl, and wherein R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from hydroxy, bromo, iodo, C_1-C_6 alkoxy, -O(C_1-C_6 alkyl), -ON(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl) (C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -COOH, -O(C_1-C_4 alkyl), -NH(C1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2 (C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), and -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein each of the foregoing C_1-C_{12} alkyl and C_1-C_{10} alkylene moieties in the definition may optionally contain one to three double or triple bonds; or R_1 and R_2, taken together with the atom to which they are attached, may form a saturated 3- to 8-membered ring which, if it is a 5- to 8-membered ring, may optionally contain one to two double bonds, and wherein one or two of the carbon atoms of said 5- to 8- membered ring may optionally be replaced, independently, by O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl or benzyl;

[0436] R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), or -SO_2 (C_1-C_4 alkyl), wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_3 may contain one double or triple bond and may optionally be substituted with from 1 to 3 substituents independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

[0437] R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n (C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein each of the foregoing C_1-C_6 alkyl moieties in the definition of R_4 may optionally be substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0438] R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl,

benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolindinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or a 3- or 8-membered cycloalkyl or 9- or 12-membered bicycloalkyl ring, wherein one or two of the carbon atoms in said ring may optionally be replaced, independently, by O, S or -N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, and wherein each of the above R_5 groups may optionally be substituted with one or more substituents, preferably with two or three substituents, independently selected from fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or with one substituent selected from hydroxy, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl), and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally be substituted with from one to two substituents independently selected from fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino and acetyl, and wherein each of the foregoing C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the definition of R_5 may optionally contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

[0439] R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, and wherein each of the foregoing (C_1-C_6)alkyl moieties in the definition of R_6 may be optionally substituted with one substituent selected from hydroxy, trifluoromethyl, amino, carboxy, amido, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano and nitro;

[0440] R_7 is hydrogen, hydroxy, fluoro, chloro, -COO(C_1-C_2 alkyl), cyano, or -CO(C_1-C_2 alkyl); and

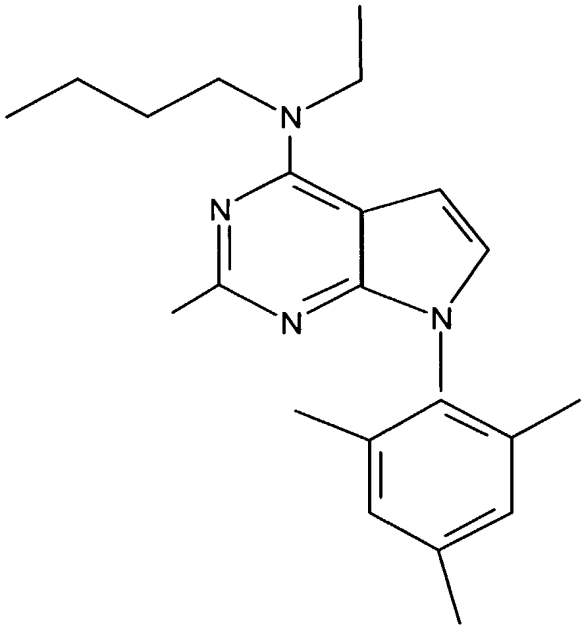
[0441] R_8 is hydrogen or C_1-C_4 alkyl;

[0442] with the proviso that:

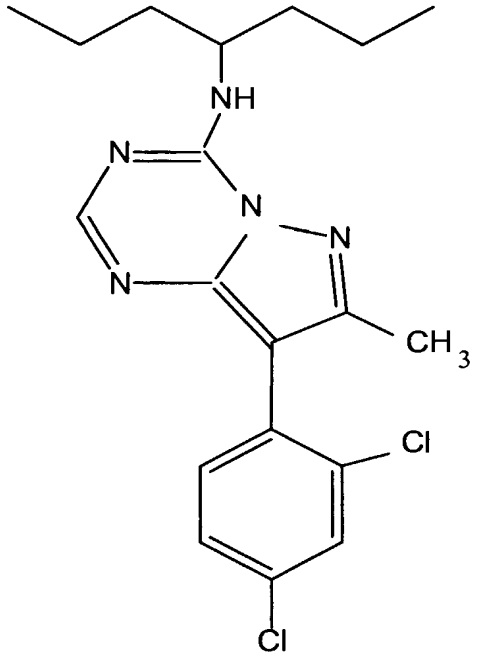
[0443] B is not a straight chain alkyl when R_5 is unsubstituted cycloalkyl, R_3 and R_4 are both hydrogen and R_6 is hydrogen or methyl; B is not NHR_2 wherein R_2 is benzyl or thienylmethyl; and B is not methylamino or hydroxyethylamino when R_5 is p-bromophenyl and R_3, R_4 and R_6 are methyl.

[0444] Suitable examples of compounds having formula VI are described in WO 94/13676, which is hereby incorporated by reference in its entirety.

[0445] In another embodiment, the corticotropin releasing factor antagonist is CP-154,526, having the formula:



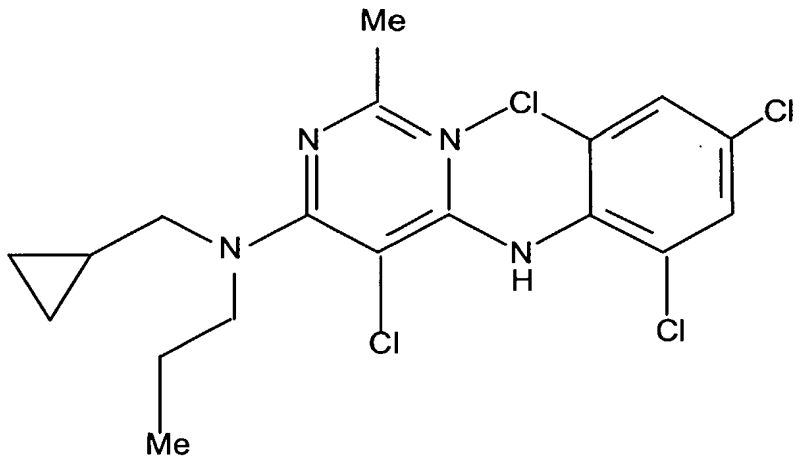
[0446] In yet another embodiment of the invention, the corticotropin releasing factor antagonist is DMP 696, having the formula:



[0447] In still another embodiment of the invention, the corticotropin releasing factor antagonist is α-helical CRF 9-41, having the sequence:

[0448] Asp-Leu-Thr-Phe-His-Leu-Arg-Glu-Met-Leu-Glu-Met-Ala-Lys-ala-Glu-Gln-Ala-Glu-Gln-Ala-Leu-Asn-Arg-Leu-Leu-Glu-Ala-NH2 (Sequence ID No.1).

[0449] In another embodiment of the invention, the corticotropin releasing factor antagonist is NBI 27914 hydrochloride, having the formula:



[0450] Generally speaking, the corticotropin releasing antagonist can be administered as a pharmaceutical composition with or without a carrier. The terms "pharmaceutically acceptable carrier" or "carrier" refer to any generally acceptable excipient or drug delivery composition that is relatively inert and non-toxic. Exemplary carriers include sterile water, salt solutions (such as Ringer's solution), alcohols, gelatin, talc, viscous paraffin, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, calcium carbonate, carbohydrates (such as lactose, sucrose, dextrose, mannose, albumin, starch), cellulose, silica gel, polyethylene glycol (PEG), dried skim milk, rice flour, magnesium stearate, and the like. Suitable formulations and additional carriers are described in Remington's Pharmaceutical Sciences, (17.sup.th Ed., Mack Pub. Co., Easton, Pa.). Such preparations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, preservatives and/or aromatic substances and the like which do not deleteriously react with the active compounds. Typical preservatives can include, potassium sorbate, sodium metabisulfite, methyl paraben, propyl paraben, thimerosal, etc. The compositions can also be combined

where desired with other active substances, e.g., enzyme inhibitors, to reduce metabolic degradation.

[0451] Moreover, the corticotropin releasing antagonist can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The method of administration can dictate how the composition will be formulated. For example, the composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, or magnesium carbonate.

[0452] In another embodiment, the corticotropin releasing antagonist can be administered intravenously, parenterally, intramuscularly, subcutaneously, orally, nasally, topically, by inhalation, by implant, by injection, or by suppository. For enteral or mucosal application (including via oral and nasal mucosa), particularly suitable are tablets, liquids, drops, suppositories or capsules. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Liposomes, microspheres, and microcapsules are available and can be used. Pulmonary administration can be accomplished, for example, using any of various delivery devices known in the art such as an inhaler. See. e.g. S. P. Newman (1984) in Aerosols and the Lung, Clarke and Davis (eds.), Butterworths, London, England, pp. 197-224; PCT Publication No. WO 92/16192; PCT Publication No. WO 91/08760. For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like.

[0453] The actual effective amounts of compound or drug can and will vary according to the specific composition being utilized, the mode of administration and the age, weight and condition of the subject. Dosages for a particular individual subject can be determined by one of ordinary skill in the art using conventional considerations.

[0454] By way of example, in one embodiment when the corticotropin releasing antagonist is α-helical CRF 9-41, the amount administered daily is typically from about 0.5 to about 3500 milligrams. In an alternative of this embodiment, the amount of α-helical CRF 9-41 administered daily is between about 1 and about 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment,

the amount of α-helical CRF 9-41 administered daily is between about 5 and about 20 milligrams/kilogram of the subject's weight.

[0455] By way of further example, in another embodiment the corticotropin releasing antagonist is antalarmin, and the amount administered daily is typically from about 50 to about 4000 miligrams. In an alternative of this embodiment, the amount of antalarmin administered daily is between about 1 and 50 milligrams/kilogram of the subject's weight. In another alternative of this embodiment, the amount of antalarmin administered daily is between about 5 and about 30 milligrams/kilogram of the subject's weight.

[0456] Moreover, the corticotropin releasing factor antagonist can be a combination of two or more different corticotropin releasing antagonists. The multiple antagonists can be administered separately or may be co-administered as a single composition and may be administered as discussed above.

[0457] By way of example, in another embodiment the corticotropin releasing antagonist is a combination of α-helical CRF 9-41 and antalarmin, and the amount of the combination antagonist administered daily is typically from about 0.1 to about 1000 μg. In an alternative of this embodiment, the amount of the combination antagonist administered daily is between about 1 and 50 milligrams/ kilogram of the subject's weight. In another alternative of this embodiment, the amount of the combination antagonist administered daily is between about 5 and about 25 milligrams/ kilogram of the subject's weight.

[0458] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711 and from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Tenth Edition (2001), Appendix II, pp. 475-493.

[0459] Generally speaking, when the composition is administered to treat an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject as soon as possible after the reduction in blood flow to the central nervous system in order to reduce the extent of ischemic damage. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 10 days after the reduction of blood flow to the central nervous system and more typically, within 24 hours. In still another embodiment, the corticotropin releasing factor antagonist and

cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours after the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours after the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours after the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours after the reduction in blood flow to the central nervous system.

[0460] Generally speaking, when the composition is administered to prevent an ischemic mediated condition, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered to the subject such that the antagonist has sufficient time to bind to the corticotropin releasing factor receptors and/or to exact its preventative effects. Typically, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered within about 24 hours before the reduction of blood flow to the central nervous system and more typically, within about 12 hours. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered from about 1 to about 12 hours before the reduction in blood flow to the central nervous system. In another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 6 hours before the reduction in blood flow to the central nervous system. In still another embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 3 to about 4 hours before the reduction in blood flow to the central nervous system. In yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 2 hours before the reduction in blood flow to the central nervous system. In still a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1 hour before the reduction in blood flow to the central nervous system. In still yet a further embodiment, the corticotropin releasing factor antagonist and cyclooxygenase-2 selective inhibitor are administered in less than about 1/2 hour before the reduction in blood flow to the central nervous system.

[0461] Moreover, the timing of the administration of the cyclooxygenase-2 selective inhibitor in relation to the administration of the corticotropin releasing factor antagonist may also vary from subject to subject. In one embodiment, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered substantially simultaneously, meaning that each agent may be administered to the subject at approximately the same time. For example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning on the same day as the beginning of the corticotropin releasing factor antagonist and extending to a period after the end of the corticotropin releasing factor antagonist. Alternatively, the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist may be administered sequentially, meaning that they are each administered at separate times during separate treatments. In one embodiment, for example, the cyclooxygenase-2 selective inhibitor is administered during a continuous period beginning prior to administration of the corticotropin releasing factor antagonist and ending after administration of the corticotropin releasing factor antagonist. Of course, it is also possible that the cyclooxygenase-2 selective inhibitor may be administered either more or less frequently than the corticotropin releasing factor antagonist. Moreover, it will be apparent to those skilled in the art that it is possible, and perhaps desirable, to combine various times and methods of administration in the practice of the present invention.

COMBINATION THERAPIES

[0462] Generally speaking, it is contemplated that the composition employed in the practice of the invention may include one or more of any of the cyclooxygenase-2 selective inhibitors detailed above in combination with one or more of any of the corticotropin releasing factor antagonists detailed above. By way of a non-limiting example, Table 4a details a number of suitable combinations that are useful in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4a.

TABLE 4a

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing Factor Antagonist
a compound having formula I	α-helical CRF 9-41
a compound having formula I	antalarmin
a compound having formula I	astressin
a compound having formula I	NBI 27914
a compound having formula I	R121919
a compound having formula I	R121920
a compound having formula I	antisauvagine-30
a compound having formula I	DMP-695
a compound having formula I	CP-154,526
a compound having formula II	α-helical CRF 9-41
a compound having formula II	antalarmin
a compound having formula II	astressin
a compound having formula II	NBI 27914
a compound having formula II	R121919
a compound having formula II	R121920
a compound having formula II	antisauvagine-30
a compound having formula II	DMP-695
a compound having formula II	CP-154,526
a compound having formula III	α-helical CRF 9-41
a compound having formula III	antalarmin
a compound having formula III	astressin
a compound having formula III	NBI 27914
a compound having formula III	R121919
a compound having formula III	R121920
a compound having formula III	antisauvagine-30
a compound having formula III	DMP-695
a compound having formula III	CP-154,526
a compound having formula IV	α-helical CRF 9-41
a compound having formula IV	antalarmin
a compound having formula IV	astressin
a compound having formula IV	NBI 27914
a compound having formula IV	R121919
a compound having formula IV	R121920
a compound having formula IV	antisauvagine-30
a compound having formula IV	DMP-695
a compound having formula IV	CP-154,526
a compound having formula V	α-helical CRF 9-41
a compound having formula V	antalarmin
a compound having formula V	astressin
a compound having formula V	NBI 27914
a compound having formula V	R121919
a compound having formula V	R121920
a compound having formula V	antisauvagine-30
a compound having formula V	DMP-695
a compound having formula V	CP-154,526

[0463] By way of further example, Table 4b details a number of suitable combinations that may be employed in the methods and compositions of the present invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4b.

TABLE 4b

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	*α*-helical CRF 9-41

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antalarmin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	astressin

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	NBI 27914

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121919

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	R121920

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	antisauvagine-30

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	DMP-695

a compound selected from the group consisting of B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B-11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B23a, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33,B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100,B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, B233, B-234, B-235, B-236, B-237, B-238, B-239, B-240, B-241, B-242, B-243 B-244, B-245, B-246, B-247, B-248, B-249, B-250, B-251, and B-252.	CP-154,526

[0464] By way of yet further example, Table 4c details additional suitable combinations that may be employed in the methods and compositions of the current invention. The combination may also include an isomer, a pharmaceutically acceptable salt, ester, or prodrug of any of the cyclooxygenase-2 selective inhibitors and/or corticotropin releasing factor antagonists listed in Table 4c.

TABLE 4c

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Celecoxib	α-helical CRF 9-41
Celecoxib	antalarmin
Celecoxib	astressin
Celecoxib	NBI 27914
Celecoxib	R121919
Celecoxib	R121920
Celecoxib	antisauvagine-30
Celecoxib	DMP-695
Celecoxib	CP-154,526
Cimicoxib	α-helical CRF 9-41
Cimicoxib	antalarmin
Cimicoxib	astressin
Cimicoxib	NBI 27914
Cimicoxib	R121919
Cimicoxib	R121920
Cimicoxib	antisauvagine-30
Cimicoxib	DMP-695
Cimicoxib	CP-154,526
Deracoxib	α-helical CRF 9-41
Deracoxib	antalarmin
Deracoxib	astressin
Deracoxib	NBI 27914
Deracoxib	R121919
Deracoxib	R121920
Deracoxib	antisauvagine-30
Deracoxib	DMP-695
Deracoxib	CP-154,526
Valdecoxib	α-helical CRF 9-41
Valdecoxib	antalarmin
Valdecoxib	astressin
Valdecoxib	NBI 27914
Valdecoxib	R121919
Valdecoxib	R121920
Valdecoxib	antisauvagine-30
Valdecoxib	DMP-695
Valdecoxib	CP-154,526
Rofecoxib	α-helical CRF 9-41
Rofecoxib	antalarmin
Rofecoxib	astressin
Rofecoxib	NBI 27914
Rofecoxib	R121919
Rofecoxib	R121920
Rofecoxib	antisauvagine-30
Rofecoxib	DMP-695
Rofecoxib	CP-154,526
Etoricoxib	α-helical CRF 9-41

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
Etoricoxib	antalarmin
Etoricoxib	astressin
Etoricoxib	NBI 27914
Etoricoxib	R121919
Etoricoxib	R121920
Etoricoxib	antisauvagine-30
Etoricoxib	DMP-695
Etoricoxib	CP-154,526
Meloxicam	α-helical CRF 9-41
Meloxicam	antalarmin
Meloxicam	astressin
Meloxicam	NBI 27914
Meloxicam	R121919
Meloxicam	R121920
Meloxicam	antisauvagine-30
Meloxicam	DMP-695
Meloxicam	CP-154,526
Parecoxib	α-helical CRF 9-41
Parecoxib	antalarmin
Parecoxib	astressin
Parecoxib	NBI 27914
Parecoxib	R121919
Parecoxib	R121920
Parecoxib	antisauvagine-30
Parecoxib	DMP-695
Parecoxib	CP-154,526
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	α-helical CRF 9-41
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antalarmin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	astressin
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	NBI 27914
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121919
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	R121920
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	DMP-695
4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide	CP-154,526
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	α-helical CRF 9-41
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antalarmin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	astressin
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	NBI 27914
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121919
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	R121920
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	antisauvagine-30
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	DMP-695
2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one	CP-154,526
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	α-helical CRF 9-41
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antalarmin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	astressin
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	NBI 27914
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121919

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	R121920
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	antisauvagine-30
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	DMP-695
N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide	CP-154,526
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	α-helical CRF 9-41
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antalarmin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	astressin
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	NBI 27914
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121919
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	R121920
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	antisauvagine-30
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	DMP-695
2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone	CP-154,526

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	α-helical CRF 9-41
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antalarmin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	astressin
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	NBI 27914
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121919
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	R121920
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	antisauvagine-30
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	DMP-695
2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid	CP-154,526
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	α-helical CRF 9-41
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antalarmin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	astressin
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	NBI 27914
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121919
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	R121920
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	antisauvagine-30

Cyclooxygenase-2 Selective Inhibitor	Corticotropin Releasing factor Antagonist
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	DMP-695
(3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone	CP-154,526
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	α-helical CRF 9-41
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antalarmin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	astressin
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	NBI 27914
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121919
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	R121920
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	antisauvagine-30
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	DMP-695
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid	CP-154,526
Lumiracoxib	α-helical CRF 9-41
Lumiracoxib	antalarmin
Lumiracoxib	astressin
Lumiracoxib	NBI 27914
Lumiracoxib	R121919
Lumiracoxib	R121920
Lumiracoxib	antisauvagine-30
Lumiracoxib	DMP-695
Lumiracoxib	CP-154,526

DIAGNOSIS OF A VASO-OCCLUSION

[0100] One aspect of the invention encompasses diagnosing a subject in need of treatment or prevention for a vaso-occlusive event. A number of suitable methods for diagnosing a vaso-occlusion may be used in the practice of the invention.

In one such method, ultrasound may be employed. This method examines the blood flow in the major arteries and veins in the arms and legs with the use of ultrasound (high-frequency sound waves). In one embodiment, the test may combine Doppler® ultrasonography, which uses audio measurements to "hear" and measure the blood flow and duplex ultrasonography, which provides a visual image. In an alternative embodiment, the test may utilize multifrequency ultrasound or multifrequency transcranial Doppler® (MTCD) ultrasound.

Another method that may be employed encompasses injection of the subject with a compound that can be imaged. In one alternative of this embodiment, a small amount of radioactive material is injected into the subject and then standard techniques that rely on monitoring blood flow to detect a blockage, such as magnetic resonance direct thrombus imaging (MRDTI), may be utilized to image the vaso-occlusion. In an alternative embodiment, ThromboView® (commercially available from Agenix Limited) uses a clot-binding monoclonal antibody attached to a radiolabel. In addition to the methods identified herein, a number of other suitable methods known in the art for diagnosis of vaso-occlusive events may be utilized.

INDICATIONS TO BE TREATED

[0465] Typically, the composition comprising a therapeutically effective amount of a cyclooxygenase-2 selective inhibitor and a therapeutically effective amount of a corticotropin releasing factor antagonist may be employed to treat a number of ischemic mediated central nervous system disorders or injuries.

[0466] In some aspects, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell. Typically the severity of damage that may be prevented will depend in large part on the degree of reduction in blood flow to the cell and the duration of the reduction. By way of example, the normal amount of perfusion to brain gray matter in humans is about 60 to 70 mL/100 g of brain tissue/min. Death of central nervous system cells typically occurs when the flow of blood falls below approximately 8-10 mL/100 g of brain tissue/min, while at slightly higher levels (i.e. 20-35 mL/100 g of brain tissue/min) the tissue remains alive but not able to function. In one embodiment, apoptotic or necrotic cell death may be prevented. In still a further embodiment, ischemic-mediated damage, such as cytoxic edema or central nervous system tissue anoxemia, may be prevented. In each embodiment, the central nervous system cell may be a spinal cell or a brain cell.

[0467] Another aspect encompasses administrating the composition to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the composition of the invention. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytoxic edema or central nervous system tissue anoxemia. The stroke may impact any area of the brain or be caused by any etiology commonly known to result in the occurrence of a stroke. In one alternative of this embodiment, the stroke is a brain stem stroke. Generally speaking, brain stem strokes strike the brain stem, which control involuntary life-support functions such as breathing, blood pressure, and heartbeat. In another alternative of this embodiment, the stroke is a cerebellar stroke. Typically, cerebellar strokes impact the cerebellum area of the brain, which controls balance and coordination. In still another embodiment, the stroke is an embolic stroke. In general terms, embolic strokes may impact any region of the brain and typically result from the blockage of an artery by a vaso-occlusion. In yet another alternative, the stroke may be a hemorrhagic stroke. Like embolic strokes, hemorrhagic stroke may impact any region of the brain, and typically result from a ruptured blood vessel characterized by a hemorrhage (bleeding) within or surrounding the brain. In a further embodiment, the stroke is a thrombotic stroke. Typically, thrombotic strokes result from the blockage of a blood vessel by accumulated deposits.

[0468] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure. By way of example, the subject may be undergoing heart surgery, lung surgery, spinal surgery, brain surgery, vascular surgery, abdominal surgery, or organ transplantation surgery. The organ transplantation surgery may include heart, lung, pancreas or liver transplantation surgery. Moreover, the central nervous system ischemic condition may occur as a result of a trauma or injury to a part of the subject's body outside the central nervous system. By way of example, the trauma or injury may cause a degree of bleeding that significantly reduces the total volume of blood in the subject's body.

Because of this reduced total volume, the amount of blood flow to the central nervous system is concomitantly reduced. By way of further example, the trauma or injury may also result in the formation of a vaso-occlusion that restricts blood flow to the central nervous system.

[0469] Of course it is contemplated that the composition may be employed to treat the central nervous system ischemic condition irrespective of the cause of the condition. In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or a cerebral embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subararachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[0470] In yet another aspect, the composition is administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, the composition may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition

[0471] In a further aspect, the invention provides treatment for subjects who are at risk of a vaso-occlusive event. These subjects may or may not have had a previous vaso-occlusive event. The invention embraces the treatment of subjects prior to a vaso-occlusive event, at a time of a vaso-occlusive event and following a vaso-occlusive event. Thus, as used herein, the "treatment" of a subject is intended to embrace both prophylactic and therapeutic treatment, and can be used either to limit or to eliminate altogether the symptoms or the occurrence of a vaso-occlusive event.

[0472] In addition to a cyclooxygenase-2 selective inhibitor and a corticotropin releasing factor antagonist, the composition of the invention may also include any agent that ameliorates the effect of a reduction in blood flow to the central nervous system. In one embodiment, the agent is an anticoagulant including thrombin inhibitors such as heparin and Factor Xa inhibitors such as warafin. In an additional embodiment, the agent is an anti-platelet inhibitor such as a GP IIb/IIIa inhibitor. In a further embodiment, the agent is selected from tissue plasminogen activator (t-PA), streptokinase, and

urokinase. Additional agents include but are not limited to, HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); ß-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

[0473] In a further aspect, the composition may be employed to reverse or lessen central nervous system cell damage following a traumatic brain or spinal cord injury. Traumatic brain or spinal cord injury may result from a wide variety of causes including, for example, blows to the head or back from objects; penetrating injuries from missiles, bullets, and shrapnel; falls; skull fractures with resulting penetration by bone pieces; and sudden acceleration or deceleration injuries. The composition of the invention may be beneficially utilized to treat the traumatic injury irrespective of its cause.

EXAMPLES

[0474] The following examples are intended to provide illustrations of the application of the present invention. The following examples are not intended to completely define or otherwise limit the scope of the invention.

EXAMPLE 1 - EVALUATION OF COX-1 AND COX-2 ACTIVITY *IN VITRO*

[0475] The COX-2 inhibitors suitable for use in this invention exhibit selective inhibition of COX-1 over COX-2, as measured by IC_{50} values when tested *in vitro* according to the following activity assays.

PREPARATION OF RECOMBINANT COX BACULOVIRUSES

[0476] Recombinant COX-1 and COX-2 are prepared as described by Gierse et al, [*J. Biochem.*, 305, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 is cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus

transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses are isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells ($2x10^8$) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses are purified by three rounds of plaque purification and high titer (10^7-10^8 pfu/mL) stocks of virus are prepared. For large scale production, SF9 insect cells are infected in 10 liter fermentors (0.5 x 106/mL) with the recombinant baculovirus stock such that the multiplicity of infection is 0.1. After 72 hours the cells are centrifuged and the cell pellet is homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate is centrifuged at 10,000xG for 30 minutes, and the resultant supernatant is stored at -80°C before being assayed for COX activity.

ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0477] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme is stopped after ten minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. The PGE2 formed is measured by standard ELISA technology (Cayman Chemical).

FAST ASSAY FOR COX-1 AND COX-2 ACTIVITY

[0478] COX activity is assayed as PGE2 formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell membranes containing the appropriate COX enzyme are incubated in a potassium phosphate buffer (0.05 M Potassium phosphate, pH 7.5, 2 µM phenol, 1 µM heme, 300 µM epinephrine) with the addition of 20 µl of 100 µM arachidonic acid (10 µM). Compounds are pre-incubated with the enzyme for 10 minutes at 25°C prior to the addition of arachidonic

acid. Any reaction between the arachidonic acid and the enzyme is stopped after two minutes at 37°C by transferring 40 µl of reaction mix into 160 µl ELISA buffer and 25 µM indomethacin. Indomethacin, a non-selective COX-2/COX-1 inhibitor, may be utilized as a positive control. The PGE_2 formed is typically measured by standard ELISA technology utilizing a PGE2 specific antibody, available from a number of commercial sources.

[0479] Each compound to be tested may be individually dissolved in 2 ml of dimethyl sulfoxide (DMSO) for bioassay testing to determine the COX-1 and COX-2 inhibitory effects of each particular compound. Potency is typically expressed by the IC_{50} value expressed as g compound/ml solvent resulting in a 50% inhibition of PGE2 production. Selective inhibition of COX-2 may be determined by the IC_{50} ratio of COX-1/COX-2.

[0480] By way of example, a primary screen may be performed in order to determine particular compounds that inhibit COX-2 at a concentration of 10 ug/ml. The compound may then be subjected to a confirmation assay to determine the extent of COX-2 inhibition at three different concentrations (e.g., 10 ug/ml, 3.3 ug/ml and 1.1 ug/ml). After this screen, compounds can then be tested for their ability to inhibit COX-1 at a concentration of 10 ug/ml. With this assay, the percentage of COX inhibition compared to control can be determined, with a higher percentage indicating a greater degree of COX inhibition. In addition, the IC_{50} value for COX-1 and COX-2 can also be determined for the tested compound. The selectivity for each compound may then be determined by the IC_{50} ratio of COX-1/COX-2, as set-forth above.

EXAMPLE 2

[0481] In the examples below, a combination therapy contains a corticotropin releasing factor antagonist with a vehicle and a COX-2 selective inhibitor. The efficacy of such combination therapy can be evaluated in comparison to a control treatment such as a placebo treatment, administration of a COX-2 inhibitor only, or administration of a corticotropin releasing factor antagonist only. By way of example, a combination therapy may contain α-helical CRF 9-41 and celecoxib, α-helical CRF 9-41 and valdecoxib, α-helical CRF 9-41 and rofecoxib, or α-helical CRF 9-41 and paracoxib. In addition, any of the above mentioned COX-2 selective inhibitors may be similarly combined with other CRF antagonists, both peptide and non-peptide, such as for example, the pyrrolopyrimidines disclosed in WO 94/13676, CP-154,526 (Schulz et. al.,

Proc. Natl. Acad. Sci. USA, Vol. 93 (1996) 10477-10482), [D-phe^{12},Nle^{21,38}]hCRF-(12-14) (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), D-phe CRF (12-14) (Lyons et al. (1991)), astressin (Gulyas et al., *Proc. Natl. Acad. Sci. USA*, Vol 92 (1995) 10575-10579), and antalarmin (Webster et al., *Endocrinology*, Vol. 137 (1996) 57475750), NBI 27914 (Chen et al., J Med. Chem. 39: 4358-4360 (1996)), R121919, R121920 (7-dipropylamino)-2,5-dimethyl-3-[2-(dimethylamino)-5-pyridyl] pyrazolo [1,5-a] pyrimidine) (Mackay et al. (2001)), and other CFR antagonists known in the art, including the monocyclic five membered and six membered ring antagonists, and antagonists from the fused bicyclic, fused tricyclic, polycyclic, and acyclic systems.

[0482] It should be noted that these are only several examples, and that any CFR antagonist in combination with any COX-2 inhibitor of the present invention may be tested as a combination therapy. The dosages of a CFR antagonist and COX-2 inhibitor in a particular therapeutic combination may be readily determined by a skilled artisan conducting the study. The length of the study treatment will vary on a particular study and can also be determined by one of ordinary skill in the art. The combination therapy may be administered for any time period necessary to treat the ischemic event. By way of example, the combination therapy may be administered for 12 weeks. The CFR antagonist and COX-2 inhibitor can be administered by any route as described herein, but are preferably administered orally or intravenously for human subjects.

[0483] The laboratory animal study can generally be performed as described in Strijbos, et al., (1994) *Brain Research*, 656: 405-408.

[0484] Briefly, the study can be performed on male, Sprague-Dawley rats ranging in size from 200 to 250 g. The rats are anesthetized with sodium pentobarbitone, and guide cannulae are implanted into the third ventricle of the brain. This is performed seven days prior to ischemia. At least four days later, the rats are subjected to a unilateral, permanent middle cerebral artery occlusion ("MCAo") under halothane anesthesia (2% in oxygen) by electrocoagulation according to a modification of the technique disclosed in Tamura et al. ((1981) *J. Cereb. Blood Flow Metab.*, 1: 53-60).Body temperature is maintained during surgery using a heated blanket.

[0485] Rats are then injected with either a vehicle (0.9% saline) or a corticotropin releasing hormone antagonist, such as, for example, α-helical CRF 9-41 (6.5 mmol; total volume 2 µl) both 30 minutes before and 10 minutes after the MCAo.

[0486] The brain tissue can then be examined histologically for the effects of combination therapy in comparison to the placebo. Neuronal damage is determined

histologically 24 hours after ischemia. 500 µm coronal brain slices are incubated with tetrazolium stain, a histological indicator of mitochondrial viability. Lesion size is then quantified by automated Seescan image analysis.

EXAMPLE 3

[0487] This laboratory animal study can generally be performed as described in Lyons, et al., (1991) *Brain Research*, 545: 339-342.

[0488] Male Winstar rats weighing 250-300 g are induced with 2.0% halothane, intubates, and ventilated with 1.0% halothane. PE-50 catheters are inserted into the femoral vein and artery, Core body temperature is monitored and maintained at 37.0± 0.5 °C. An intraventricular injection of α-helical CRF 9-41 is administered 0.80 mm posterior, 1.50 mm lateral to the bregma and 3.80 mm deep. Fifteen minutes after injection, transient forebrain ischemia is produced for a 10 minute period by the temporary occlusion of both common carotid arteries and phlebotomizing the rat to a MABP of 50 mm Hg. After 10 minutes of ischemia, previously withdrawn and heparinized blood was infused via the femoral venous catheter and cerebral blood flow is restored by removal of the carotid artery clips. Animals are then monitored under 1.0% halothane for a 1 hour period after reperfusion (restoration of carotid blood flow).

[0489] Seven groups of five animals each are studied. Three groups act as control groups: one normal control group, one ischemic control group, and one ischemic vehicle group. The remaining four groups receive α-helical CRF 9-41 in doses of 0.1, 1.0, 10.0, or 100.0 µg in 0.9 & BaCl, the volume of each injection being 5 µl. Arterial blood samples are taken and MABP is observed and recorded as follows: 10 minutes prior to injection of α-helical CRF 9-41; after 10 minutes of ischemia just prior to reperfusion; and 30 minutes following reperfusion.

[0490] Seven days post-op, each rat is anesthetized with 2.0% halothane and the brain fixed *in situ* with 40% formaldehyde/glacial acetic acid/methanol, 1:1:8 via transcardiac perfusion after briefly washing out the cephalic circulation with heparinized 0.9% NaCl for 45 seconds. The brains are then sectioned 7mm posterior to the rostral tip of the frontal lobes and 10µm paraffin sections are stained using hematoxylin and eosin. Hippocampal regions CA1-medial, CA1-lateral, CA3, and CA4 are examined bilaterally under light microscopy using an ocular grid with magnification X 400. Ten 100 X 100 µm area are analyzed in each hippocampal region. Neurons displaying a normal nucleus, cytoplasmic staining, and configuration are counted as living cells, as

opposed to pyknotic, hyperchromatic, and shrunken neurons that would be counted as dead cells.

[0491] The number of surviving neurons and dead neurons are compared to determine the efficacy of the combination therapy. Furthermore, the $PaCO_2$, PaO_2, pH_a, MABP, serum glucose, and core body temperatures among the rats representing the various control and experimental groups are compared to determine possible side effects of the therapy or the procedures used.

EXAMPLE 4

[0492] This laboratory animal study can generally be performed as described in Mackay et al., (2001) *J. Cerebral Blood Flow and Metabolism* 21:1208-1214.

[0493] Brain and plasma levels of R121920 are determined in a number of nonoccluded male Sprague–Dawley rats weighing 280 to 340 g. A skilled artisan can readily determine the appropriate number of animals to be used for a particular experiment. R121920 in a vehicle of water is administered to each of the rats as a single intravenous (IV) dose of 10 mg/kg. An equal number of the rats are killed at 2, 5, 15, 30, 60, 120, and 240 minutes subsequent to the administration of R121920. Brains are rapidly removed, flash frozen in liquid nitrogen, and stored at -70°C until analysis. 200 μL terminal blood samples are collected into tubes containing EDTA and are promptly centrifuged for 1.5 minutes at 10,000 g. The plasma is extracted, flash frozen in liquid nitrogen, and stored at –70°C until analysis. In order to quantify the concentration of R121920 in plasma, 150 μL acetonitrile is added to 50 μL plasma to precipitate protein, and the sample is centrifuged. The supernatant is collected and dried in a Speed Vac at room temperature. In order to prepare brain sample tissue, brain tissue is homogenized in 1 mL saline solution. Protein is precipitated by adding 3 vol acetonitrile to the sample solution. After reconstitution, all samples are analyzed in a reverse phase HPLC-UV system. The concentrations of R121920 in the samples is predicted from the linear regression of an external calibration curve of five spiked matrix standards.

[0494] All rats are initially anesthetized with a mixture of 5% halothane, 30% oxygen, and 70% nitrous oxide in an induction chamber and maintained thereafter with a nitrous oxide/oxygen mixture (70%:30%) containing 1.0% to 1.5% halothane administered through a face mask. Body temperature is monitored during the surgical

procedure by a rectal thermometer. The rats are maintained at a normothermic body temperature (37 °C ± 1°C) by use of a heating blanket controlled by the thermometer.

SUBTEMPORAL MIDDLE CEREBRAL ARTERY OCCLUSION MODEL

[0495] Permanent focal ischemia is induced in male Fischer 344 rats (240 to 280 g) through a subtemporal approach, as described in Tamara et al., (1981) *J. Cereb. Blood Flow Metab.* 1: 53-60. Briefly, the craniectomy is performed at the level where the MCA crosses the lateral olfactory tract. The dura is opened, and the artery is exposed and occluded by bipolar diathermy from its origin to the point where it crosses the inferior cerebral vein. All visible lenticulostriate branches are also occluded. The artery is transected to confirm complete occlusion and to prevent recanalization. The incision sites are closed, and the animals are allowed to recover from the anesthesia.

[0496] R121920 (10 mg/kg or 20 mg/kg) is administered as an initial bolus IV dose at the time of the onset of ischemia, followed by subsequent subcutaneous (SC) injections of R121920 (5 mg/kg or 10mg/kg, respectively) at hourly intervals thereafter for a period of 4 hours. Control rats are injected with a water vehicle (1 mL/kg) at the same time points.

[0497] The rats are killed 24 hours subsequent to MCA occlusion, the brains are removed, and 500 μm coronal sections are cut from the frontal pole on a vibratome. Brain sections are incubated in a 2% solution of triphenyl tetrazolium chloride at 37°C for 30 minutes to stain for viable tissue. Infarcted regions in the hemisphere, the cortex, and the striatum on each of the sections are delineated and transcribed onto scale diagrams and quantified by automated image analysis. The infarct volume for each of the brain regions is computed by summing the areas of damage from each section and multiplying them by the distance between the sections.

INTRALUMINAL SUTURE MIDDLE CEREBRAL ARTERY OCCLUSION MODEL.

[0498] The left middle cerebral artery (MCA) is permanently occluded in a number of male Sprague-Dawley rats weighing 280 to 340 g through a cervical carotid approach using the intraluminal suture technique in male as described in detail in Zea Longa et al., (1989) *Stroke* 20: 84-91. Briefly, the common carotid, the external carotid, and the internal carotid arteries are exposed via a midline cervical incision performed under an operating microscope. A 30-mm length of 3–0 monofilament nylon suture with tip heat-blunted and coated with poly-l-lysine solution (Belayev et al.,(1996) *Stroke* 27:

1616-1622) is advanced from the external carotid artery into the lumen of the internal carotid artery until mild resistance is felt (typically 19 to 20 mm depending upon the body weight of the rat), resulting in the occlusion of the origin of the MCA. After closure of the incision, the rats are allowed to recover from anesthesia.

[0499] R121920 (10 mg/kg) is administered as an IV injection at the time of MCA occlusion, followed by additional IV injections of R121920 (10 mg/kg) at 1, 2, 3 and 4 hours subsequent thereto. Control rats are injected with a water vehicle at the same time points. The period of neuroprotective effect of R121920 is examined by delaying induction of the dosing regimen to 0, 0.5, and 1 hour after occlusion of the MCA.

[0500] Twenty-four hours subsequent to MCA occlusion, the rats are killed and the brains are removed and frozen in isopentane at –40°C. Brains are cut into 20-μm serial coronal sections at 12 equidistant levels (1 mm apart, covering the entire forebrain), are fixed for 10 minutes in 4% paraformaldehyde, and are stained with hematoxylin and eosin. The sections, corresponding to 12 stereotactically predetermined coronal planes of the brain from anterior +12.7 mm to anterior +1.7 mm relative to the interaural line (Paxinos and Watson, *The rat brain in stereotaxic coordinates.* San Diego, CA: Academic Press), are examined using a light microscope. Areas of ischemic damage are delineated and transcribed onto scale diagrams of a normal forebrain at each of the 12 coronal planes. Infarcted areas are quantified using a computer-based image analysis system, and the total volumes of ischemic tissue for each brain are derived from integration of the areas of damage in the 12 planes and the known stereotactic coordinates of the planes. The volumes of the cerebral hemispheres ipsilateral and contralateral to the occluded MCA are determined from the stained histologic sections by assessment of the total surface area at the same coronal planes as used for assessing areas of ischemic damage. The difference between the two hemispheres provide a measure of brain swelling.

[0501] It should be noted that all of the above-mentioned procedures can be modified for a particular study, depending on factors such as a drug combination used, length of the study, subjects that are selected, etc. Such modifications can be designed by a skilled artisan without undue experimentation.

WHAT IS CLAIMED IS:

1. A method for treating a stroke, the method comprising:

(a) diagnosing a subject in need of treatment for a stroke; and

(b) administering to the subject a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a corticotropin releasing factor antagonist or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC_{50} to COX-2 IC_{50} not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

5. The method of claim 1 wherein the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

6. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered substantially simultaneously.

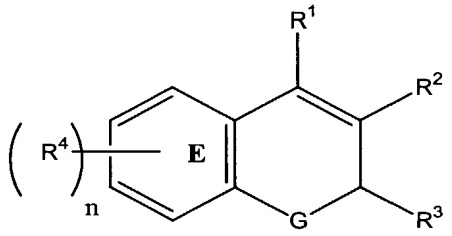
7. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor and the corticotropin releasing factor antagonist are administered sequentially.

8. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is administered to the subject in an amount of about 0.1 to about 20 mg/kg body weight per day.

9. The method of claim 1 wherein the corticotropin releasing factor antagonist is administered to the subject in an amount of about 1 to about 50 milligrams per kilogram of the subject's weight per day.

10. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(I)

wherein:

n is an integer which is 0, 1, 2, 3 or 4;

G is O, S or NR^a;

R^a is alkyl;

R^1 is selected from the group consisting of H and aryl;

R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

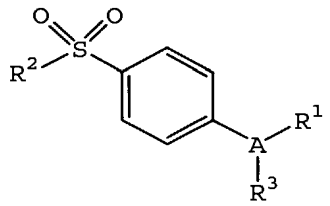
each R^4 is independently selected from the group consisting of H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl,

heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R^4 together with the carbon atoms to which it is attached and the remainder of ring E forms a naphthyl radical; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

11. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof of the formula:



wherein:

A is selected from the group consisting of a partially unsaturated or unsaturated heterocyclyl ring and a partially unsaturated or unsaturated carbocyclic ring;

R^1 is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^1 is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^2 is selected from the group consisting of methyl and amino; and

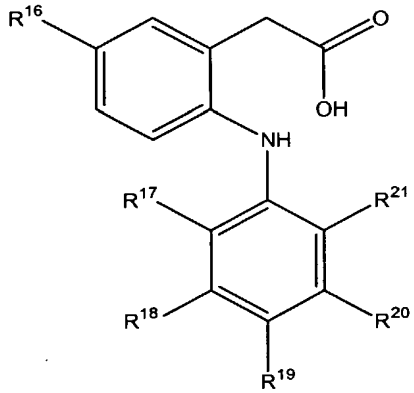
R^3 is selected from the group consisting of H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl,

alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl,
N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of *α*-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

12. A composition comprising:

(a) a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof having the formula:



(III)

wherein:

R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl, provided, however, that each of R^{17}, R^{18}, R^{20} and R^{21} is not fluoro when R^{16} is ethyl and R^{19} is H; and

(b) a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

13. A composition comprising a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and a corticotropin releasing factor antagonist selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

14. The composition of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, cimicoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, and parecoxib, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, and the corticotropin releasing factor antagonist is selected from the group consisting of α-helical CRF 9-41, antalarmin, 5-Chloro-*N*-(cyclopropylmethyl)-2-methyl-*N*-propyl-*N'*-(2,4,6-trichlorophenyl)-4,6-pyrimidinediamine hydrochloride, astressin, NBI 27914, R121919, R121920, antisauvagine-30, DMP-695, D-PheCRF 12-41, N-[3-(2,4-dichlorophenyl)-5-methylisoxazolo[4,5-d]-pyrimidin-7-yl]-N-(1-ethylpropyl)amine, CP-154,526, DMP 696, and NBI 27914 hydrochloride, or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

pha4279.ST25.txt
SEQUENCE LISTING

<110> Pharmacia Corporation
Arneric, Stephen

<120> COMPOSITIONS OF A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND A CORTICOTROPIN RELEASING FACTOR ANTAGONIST FOR THE TREATMENT OF ISCHEMIC MEDIATED CENTRAL NERVOUS SYSTEM DISORDERS OR INJURY

<130> PHA 4279. 2 (01572/1/PCT; PC27945A)

<150> US 60/498,148
<151> 2003-08-27

<160> 1

<170> PatentIn version 3.1

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20 25

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/04, A61K 31/505 // (C07D 487/04, 239:00, 231:00) (C07D 487/04, 251:00, 231:00) (C07D 487/04, 249:00, 239:00) (C07D 487/04, 251:00, 249:00)

A1

(11) International Publication Number: **WO 98/03510**

(43) International Publication Date: 29 January 1998 (29.01.98)

(21) International Application Number: PCT/US97/13072

(22) International Filing Date: 23 July 1997 (23.07.97)

(30) Priority Data:

60/023,290	24 July 1996 (24.07.96)	US
08/686,047	24 July 1996 (24.07.96)	US
Not furnished	23 July 1997 (23.07.97)	US

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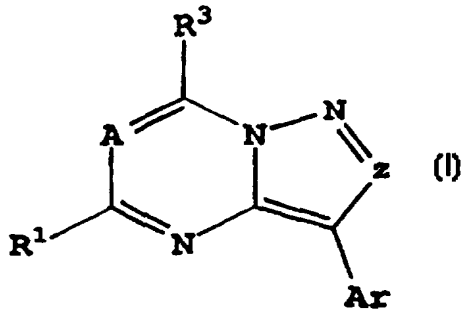
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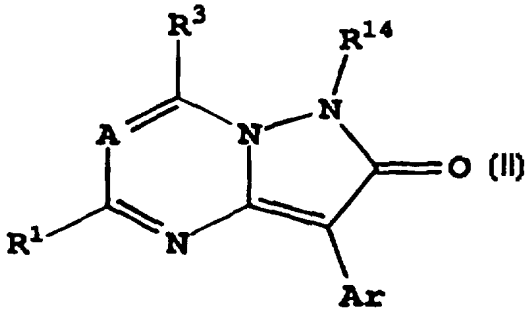
(81) Designated States: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: AZOLO TRIAZINES AND PYRIMIDINES



(I)



(II)

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) or (II) and their use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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TITLE

AZOLO TRIAZINES AND PYRIMIDINES

FIELD OF THE INVENTION

This invention relates a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress, by administration of certain [1,5-*a*]-pyrazolo-1,3,5-triazines, [1,5-*a*]-1,2,3-triazolo-1,3,5-triazines, [1,5-*a*]-pyrazolo-pyrimidines and [1,5-*a*]-1,2,3-triazolo-pyrimidines.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC)-derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (**1983**); W. Vale et al., *Science* 213:1394 (**1981**)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De Souza et al., *J.*

Neurosci. 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (**1984**); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (**1987**); R.D. France et al., *Biol. Psychiatry* 28:86 (**1988**); M. Arato et al., *Biol Psychiatry* 25:355 (**1989**)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (**1988**)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (**1984**); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (**1984**); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (**1986**)]. Preclinical studies in rats and non-human primates provide additional support for the

hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (**1989**)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (**1982**); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (**1986**)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (**1987**), *Brain Research Reviews* 15:71 (**1990**)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (**1985**); K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (**1986**)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-

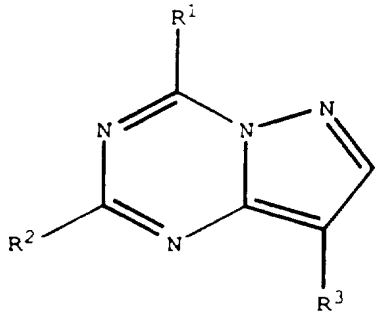
dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α-helical CRF_{9-41}) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several publications describe corticotropin releasing factor antagonist compounds and their use to treat psychiatric disorders and neurological diseases. Examples of such publications include DuPont Merck PCT application US94/11050 , Pfizer WO 95/33750, Pfizer WO 95/34563, Pfizer WO 95/33727 and Pfizer EP 0778 277 A1.

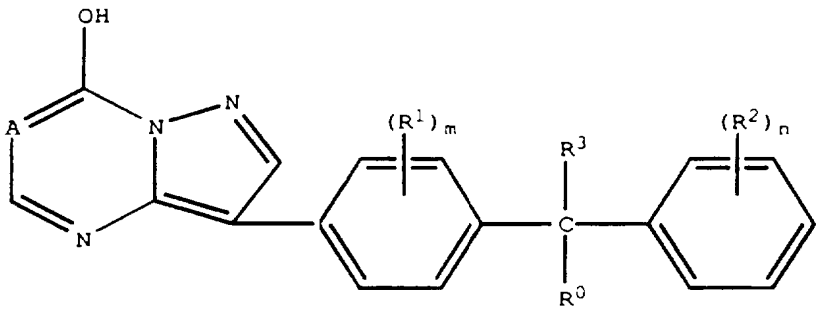
Insofar as is known, [1,5-*a*]-pyrazolo-1,3,5-triazines, [1,5-*a*]-1,2,3-triazolo-1,3,5-triazines, [1,5-*a*]-pyrazolo-pyrimidines and [1,5-*a*]-1,2,3-triazolo-pyrimidines, have not been previously reported as corticotropin releasing factor antagonist compounds useful in the treatment of psychiatric disorders and neurological diseases. However, there have been publications which teach some of these compounds for other uses.

For instance, EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



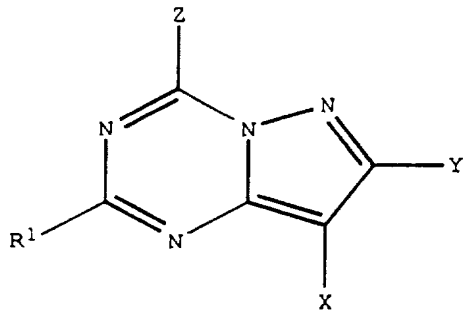
where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula



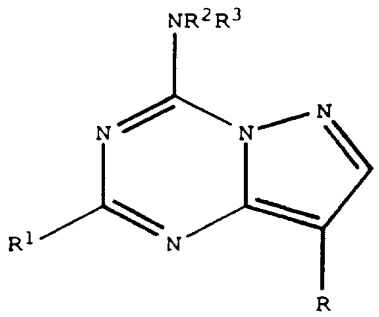
where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

US 3,910,907 (ICI, 1975) discloses pyrazolotriazines of the formula:



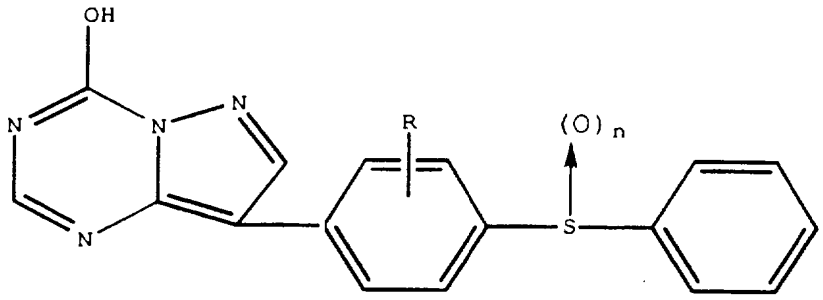
where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the formula:



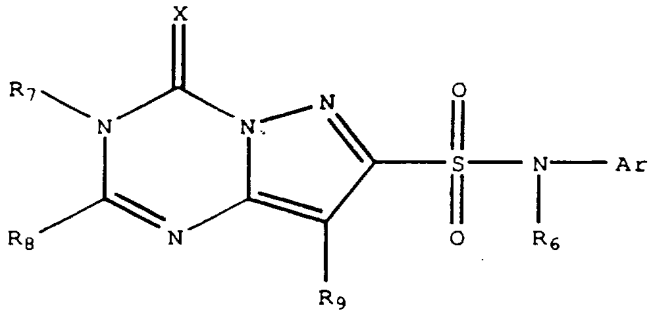
where R^1 is H or alkyl, R^2 is H or alkyl, R^3 is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



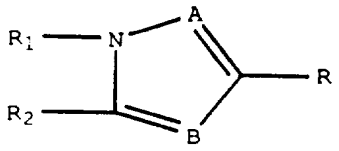
where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

US 4,892,576 discloses pyrazolotriazines of the formula

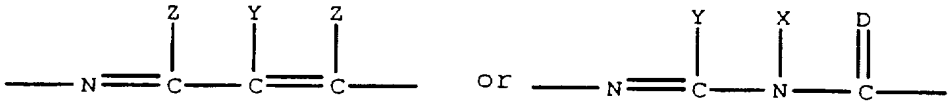


where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R_6-R_8 are H, alkyl, etc., and R_9 is H, alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal compound of the formula

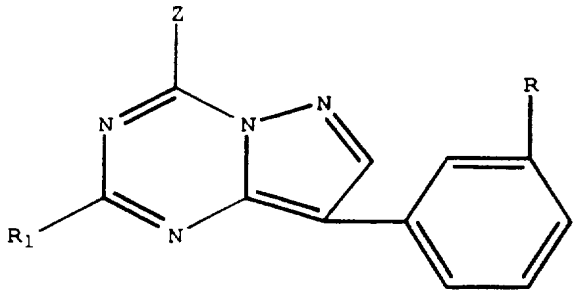


where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 can be taken together to form



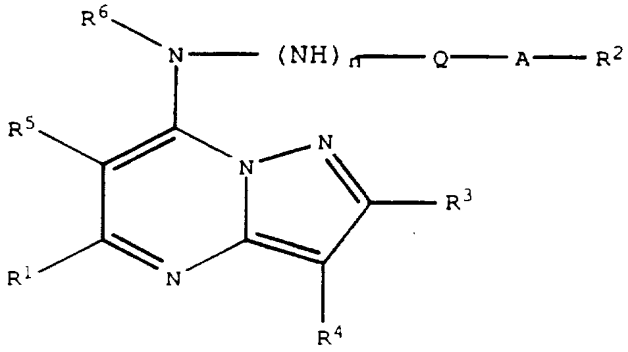
where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



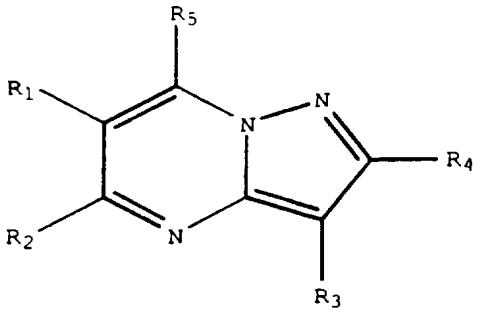
where Z is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, $NH(n\text{-}C_4H_9)$, or $N(C_2H_5)_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula



where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R^1 is H, alkyl, etc., R^2 is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R^3 is H, alkyl or phenyl, R^4 is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R^5 and R^6 are H or alkyl.

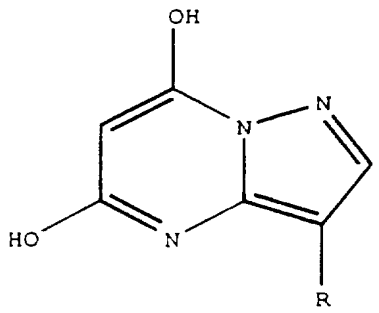
EP 0 591 528 (Otsuka,1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula



where R_1, R_2, R_3 and R_4 are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R_5

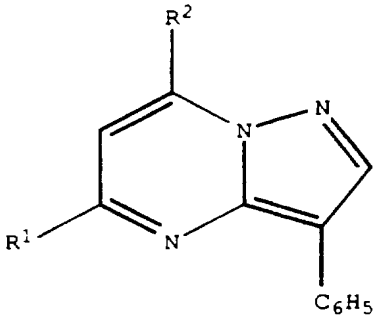
is SR_6 or NR_7R_8, R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula



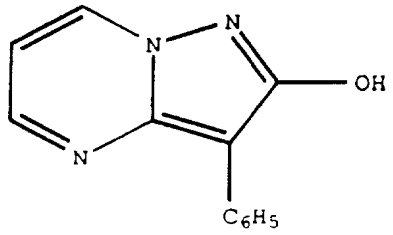
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula

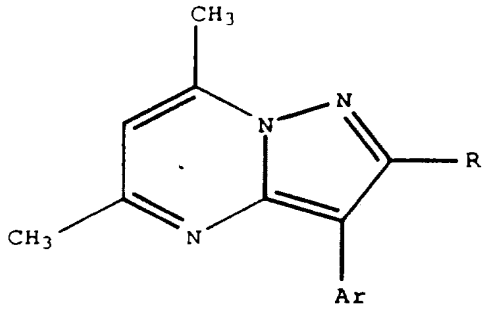


where R^1 is CF_3, C_2F_5, or C_6H_4F, and R^2 is CH_3, C_2H_5, CF_3, or C_6H_4F.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-*a*]pyrimidine of the formula



Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-*a*]pyrimidines of the formula



where R is NH2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

Other references which disclose azolopyrimidines inclued EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985).

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress;

stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

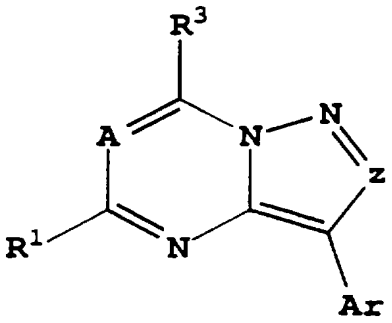
According to another aspect, the present invention provides novel compounds of Formulae (1) and (2) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of Formulae (1) and (2), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

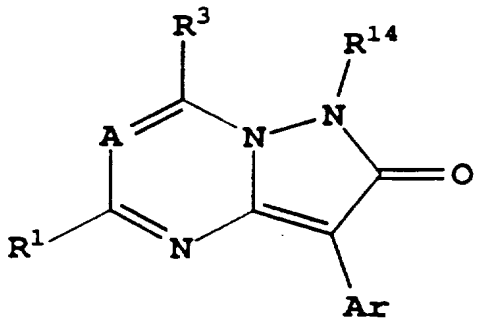
DETAILED DESCRIPTION OF INVENTION

[1] The present invention comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by

antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10}

cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

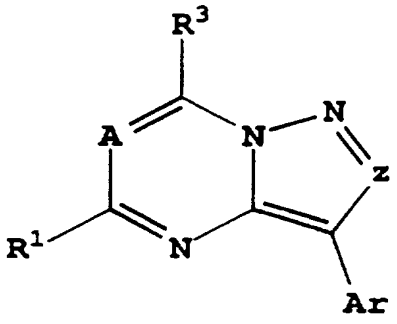
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

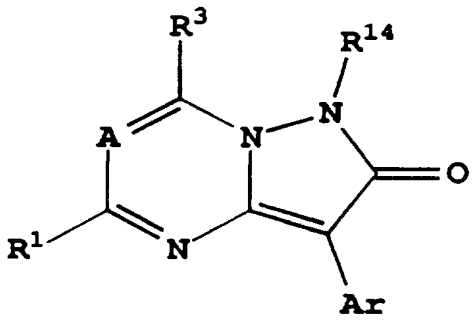
[2] Preferred methods of the present invention are methods in wherein in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[3] Further preferred methods of the above invention are methods wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

[4] The present invention comprises compounds of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

$-H$, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3

substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, -aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine; N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected

at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

with the provisos that:

(1) when A is N, Z is CR^2, R^2 is H, R^3 is $-OR^7$ or $-OCOR^{13}$, and R^7 is H, then R^1 is not H, OH or SH;

(2) when A is N, Z is CR^2, R^1 is CH_3 or C_2H_5, R^2 is H, and R^3 is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, then Ar is not phenyl or m-CH_3-phenyl;

(3) when A is N, Z is CR^2, R^2 is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R^3 is $NR^{6a}R^{7a}$, then R^{6a} and R^{7a} are not H or alkyl;

(4) when A is N, Z is CR^2, and R^2 is $SO_2NR^6R^7$, then R^3 is not OH or SH;

(5) when A is CR and Z is CR^2, then R^2 is not-$NR^6SO_2R^7$ or $-SO_2NR^6R^7$;

(6) when A is N, Z is CR^2 and R^2 is $-NR^6SO_2R^7$ or $-SO_2NR^6R^7$, then R^3 is not OH or SH;

(7) when A is N, Z is CR^2, R^1 is methyl or ethyl, R^2 is H, and R^3 is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7,

iso-C_3H_7, SH, SCH_3, $NH(n\text{-}C_4H_9)$, or $N(C_2H_5)_2$, then Ar is not unsubstituted phenyl or m-methylphenyl;

(8) when A is CR, Z is CR^2, R^2 is H, phenyl or alkyl, R^3 is NR^8COR^7 and Ar is phenyl or phenyl substituted with phenylthio, then R^7 is not aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocycly(C_1-C_4 alkyl);

(9) when A is CR, Z is CR^2, R^2 is H or alkyl, Ar is phenyl, and R^3 is SR^{13} or $NR^{6a}R^{7a}$, then R^{13} is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or

(10) when A is CH, Z is CR^2, R^1 is OR^{11}, R^2 is H, R^3 is OR^7, and R^7 and R^{11} are both H, then Ar is not phenyl, p-Br-phenyl, p-Cl-phenyl, p-$NHCOCH_3$-phenyl, p-CH_3-phenyl, pyridyl or naphthyl;

(11) when A is CH, Z is CR^2, R^2 is H, Ar is unsubstituted phenyl, and R^3 is CH_3, C_2H_5, CF_3 or C_6H_4F, then R_1 is not CF_3 or C_2F_5;

(12) when A is CR, R is H, Z is CR^2, R^2 is OH, and R^1 and R^3 are H, then Ar is not phenyl;

(13) when A is CR, R is H, Z is CR^2, R^2 is OH or NH_2, R^1 and R^3 are CH_3, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

[5] Preferred compounds of the above invention are compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4

alkoxyalkyl or $SO_2(C_1-C_4$ alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{6a} is unsubstituted C_1-C_4 alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl; and (2) A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1-C_4$ alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{7a} is unsubstituted C_1-C_4 alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl.

[6] Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

[7]. Preferred compounds of the above invention also include compounds of Formulae (1) and (2) and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

[11] More preferred compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

[12] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[13] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[14] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[15] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[16] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

[17] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[18] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[19] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-; and

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[20] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from

C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[21] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is selected from:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[22] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[23] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$,

$R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[24] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[25] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[26] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, -COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[27] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[28] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl,

cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[29] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[30] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[31] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

[32] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

[33] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

[34] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[35] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[36] More preferred compounds of the above invention also include compounds and isomers thereof,

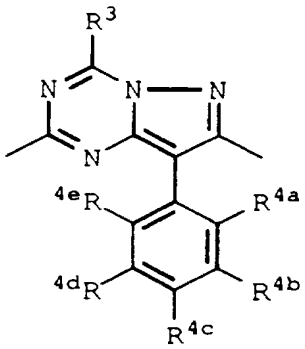
stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

- $-C_3-C_6$ cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,
- -aryl,
- -heteroaryl or
- -heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

[37] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[38] Specifically preferred compounds of the above invention are compounds of Formula (50)



FORMULA (50)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:

a compound of Formula (50) wherein R^3 is $-NHCH(n-Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)(n-Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-(n-Pr)(CH_2cPr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n-Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Pr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-OEt$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)(CH_2cPr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Bu)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(c\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NH(CH_2OMe)(CH_2-iPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OEt)(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2c\text{-}Pr)$ (n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OH)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (50) wherein R^3 is $N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

[39] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[40] More specifically preferred is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[41] More preferred are compounds of the above invention are compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is CR.

[42] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[43] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[44] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[45] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[46] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

[47] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is

phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

[48] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

[49] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

[50] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[51] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

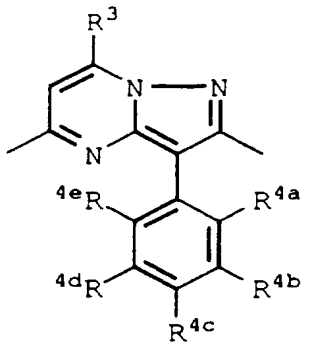
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

[52] More preferred compounds of the above invention also include compounds and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

[53] Specifically preferred compounds of the above invention are compounds of Formula (51)



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Bu)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH (n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH (n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

[54] More specifically preferred is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[55] More specifically preferred is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

[56] More specifically preferred is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also provides pharmaceutical compositions comprising compounds of Formulae (1) and (2) and a pharmaceutically acceptable carrier.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. Commonly used abbreviations have the following meanings: Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl. The prefix "n" means a straight chain alkyl. The prefix "c" means a cycloalkyl. The prefix "(*S*)" means the S enantiomer and the prefix "(*R*)" means the R enantiomer. Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the

like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis,

Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of Formulae (1) and (2). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing

Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

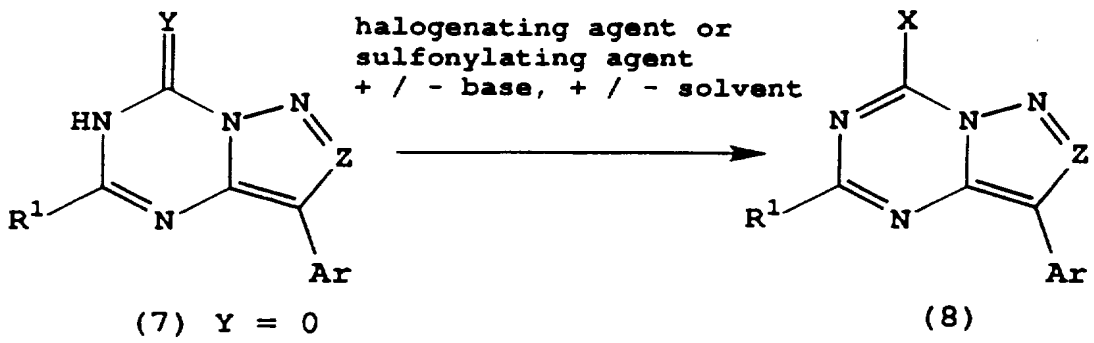
"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

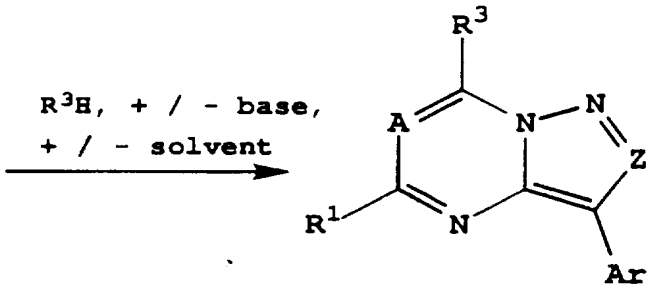
Syntheses

Some compounds of Formula (1) may be prepared from intermediate compounds of Formula (7), using the procedures outlined in Scheme 1:

SCHEME 1



(7) Y = O (8)



(1) A = N

Compounds of Formula (7) (where Y is O) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (8) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal

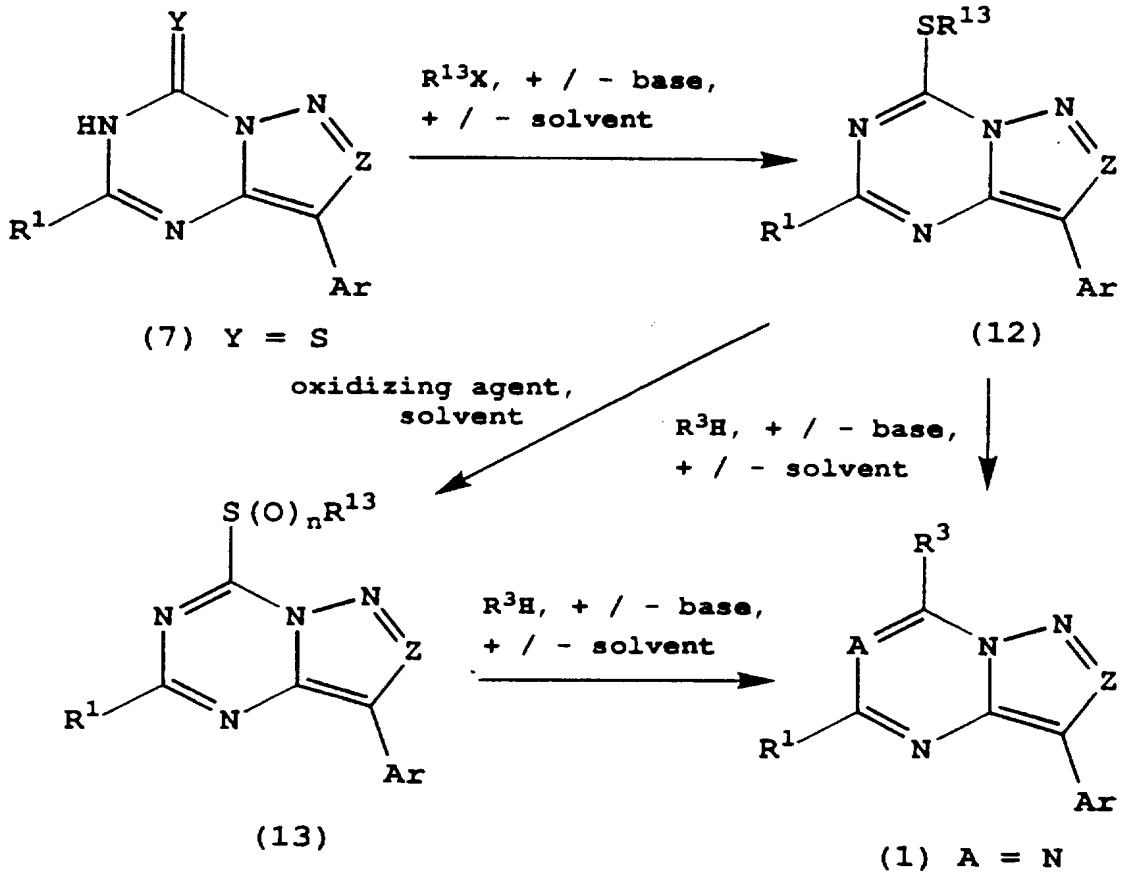
hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (8) may be reacted with compounds of Formula R^3H (where R^3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80 to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Scheme 2 delineates the procedures for converting intermediate compounds of Formula (7) (where Y is S) to some compounds of Formula (1).

SCHEME 2



Compounds of Formula (7) (where Y is S) may be treated with an alkylating agent $R^{13}X$ (where R^{13} is defined as above, except R^{13} is not aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium

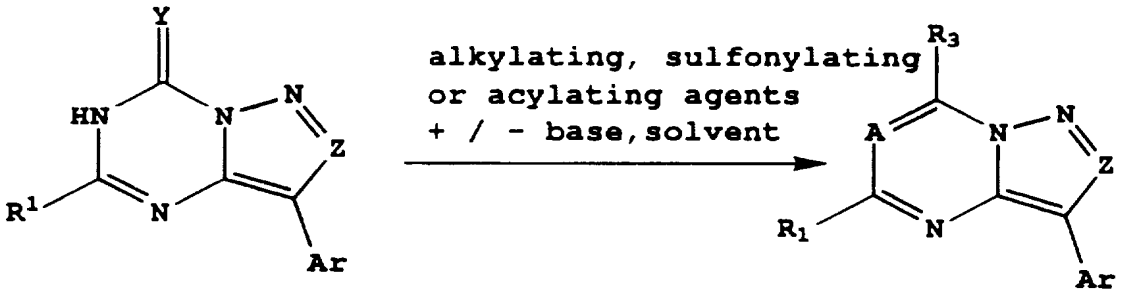
bis(trimethylsilyl)amide), trialkyl amines (prefereably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme 1 above. Alternatively, compounds of Formula (12) (Formula (1) where R^3 is SR^{13}) may be oxidized to compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) by treatment with an oxidizing agent in the presence of an inert solvent at temperatures ranging from -80°C to 250°C. Oxidizing agents include, but are not limited to, hydrogen peroxide, alkane or aryl peracids (preferably peracetic acid or m-chloro-perbenzoic acid), dioxirane, oxone, or sodium periodate. Inert solvents may include, but are not limited to, alkanones (3 to 10 carbons, preferably acetone), water, alkyl alcohols (1 to 6 carbons), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens

(preferably dichloromethane) or combinations thereof. The choices of oxidant and solvent are known to those skilled in the art (cf. Uemura, S., Oxidation of Sulfur, Selenium and Tellurium, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 7, 762-769). Preferred reaction temperatures range from -20°C to 100°C. Compounds of Formula (13) (Formula (1) where R^3 is $S(O)_nR^{13}$, n is 1,2) may then be reacted with compounds of Formula R^3H to give compounds of Formula (1), using the same conditions and reagents as were used for the conversion of compounds of Formula (8) to compounds of Formula (1) as outlined for Scheme (1) above.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be prepared from compounds of Formula (7), where Y is NH, by the procedures depicted in Scheme 3.

SCHEME 3



(7) Y = NH

(1)

A = N;
R_3 = NR^6R^7, NR^8COR^7, $N(COR^7)_2$, $NR_8CONR^6R^7$, $NR_8CO_2R_{13}$

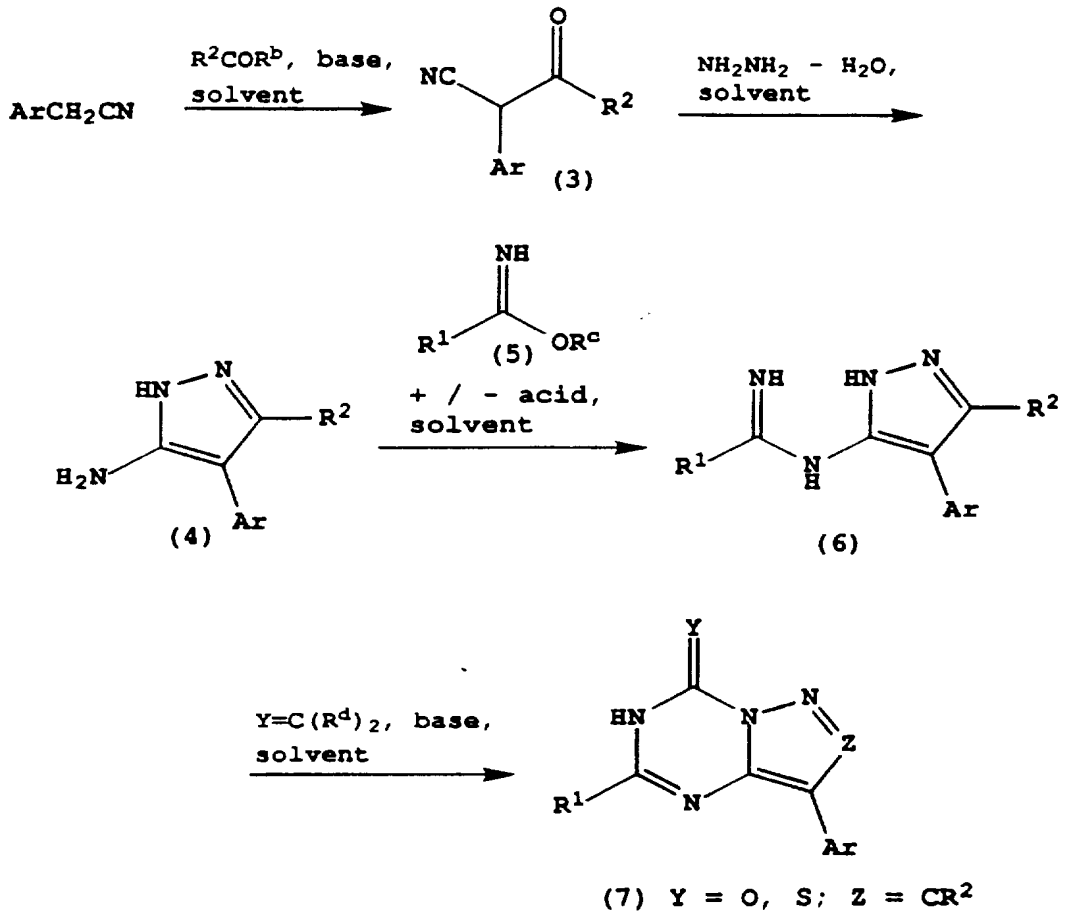
Reaction of compounds of Formula (7), where Y is NH, with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with

combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides,

heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Scheme 4 delineates procedures, which may be employed to prepare intermediate compounds of Formula (7), where Y is O, S and Z is CR^2.

SCHEME 4



Compounds of the formula $ArCH_2CN$ are reacted with compounds of the formula R^2COR^b, where R^2 is defined above and R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78°C to 200°C to afford compounds of Formula (3). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (3) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (4). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Compounds of Formula (4) may be reacted with compounds of Formula (5) (where R^c is alkyl (1-6 carbons)) in the presence or absence of an acid in the presence of an inert solvent at temperatures ranging from 0°C to 200°C to produce compounds of Formula (6). Acids may include, but are

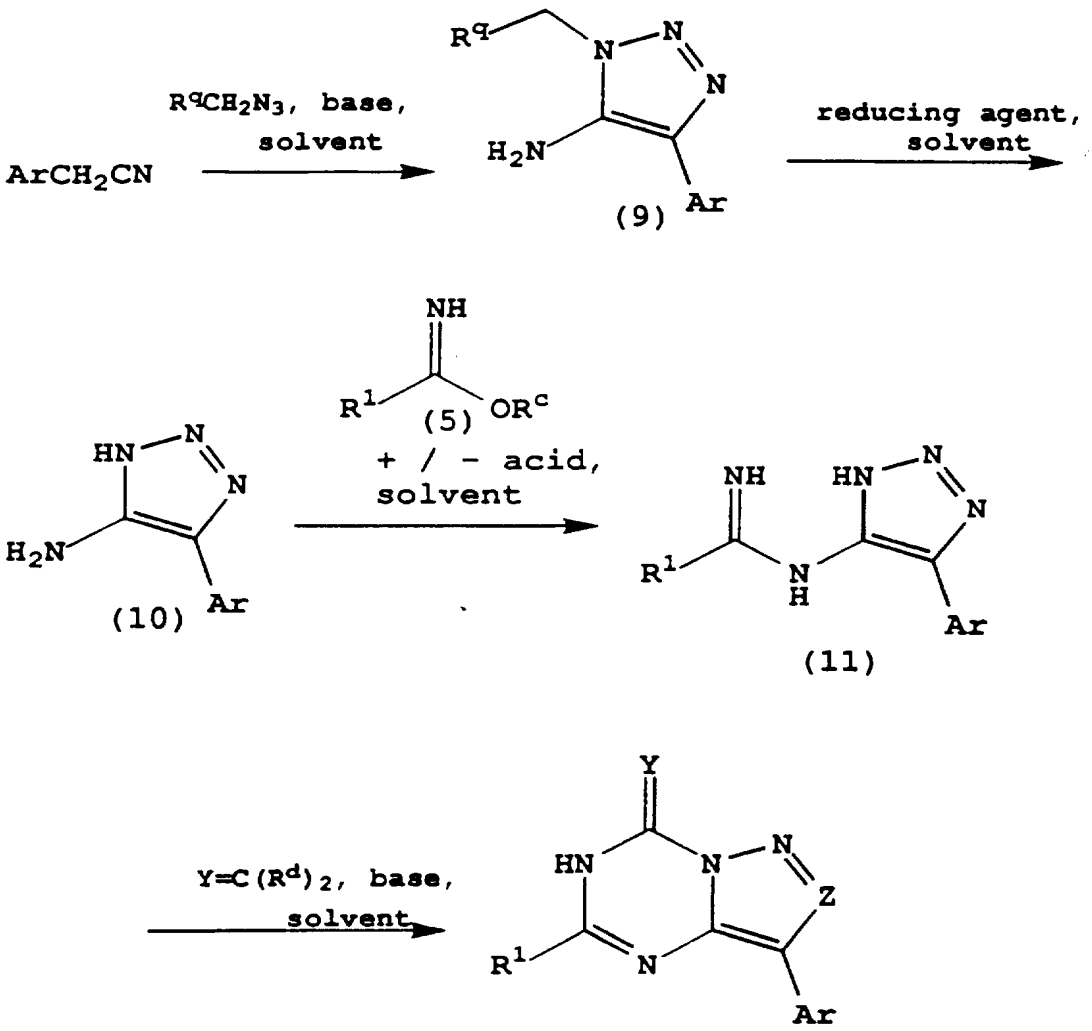
not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, water, alkanenitriles (1 to 6 carbons, preferably acetonitrile), halocarbons of 1 to 6 carbons and 1 to 6 halogens (preferably dichloromethane or chloroform), alkyl alcohols of 1 to 10 carbons (preferably ethanol), dialkyl ethers (4 to 12 carbons, preferably diethyl ether or di-isopropylether) or cyclic ethers such as dioxan or tetrahydrofuran. Preferred temperatures range from ambient temprature to 100°C.

Compounds of Formula (6) may be converted to intermediate compounds of Formula (7) by treatment with compounds $C=Y(R^d)_2$ (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent at reaction temperatures from -50°C to 200°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkali metal carbonates, alkali metal hydroxides, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably

dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred temperatures are 0°C to 150°C.

Intermediate compounds of Formula (7), where Z is N, may be synthesized according the methods outlined in Scheme 5.

SCHEME 5



Compounds of $ArCH_2CN$ are reacted with compounds of Formula $R^qCH_2N_3$ (where R^q is a phenyl group optionally substituted by H, alkyl (1 to 6 carbons) or alkoxy (1 to 6 carbons) in the presence or absence of a base in an inert solvent at temperatures ranging from 0°C to 200°C to generate compounds of Formula (9). Bases may include, but are not limited to, alkali metal hydrides

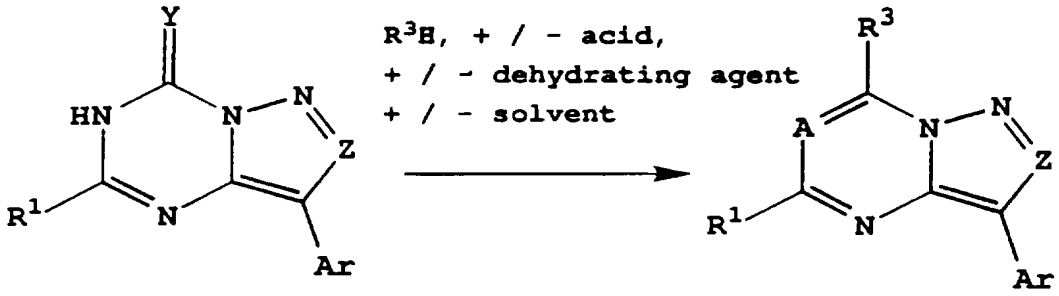
(preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide, sodium ethoxide or potassium t-butoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from ambient temperature to 100°C.

Compounds of Formula (9) may be treated with a reducing agent in an inert solvent at -100°C to 100°C to afford products of Formula (10). Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO_2, Pt-on-carbon, Rh-on-alumina or Raney nickel, (b) alkali metals (preferably sodium) in combination with liquid ammonia or (c) ceric ammonium nitrate. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides

(preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). The preferred reaction temperatures are -50°C to 60°C. Compounds of Formula (9) are then converted to compounds of Formula (7) (where Z is N) via intermediates of Formula (11) using the reagents and reaction conditions outlined in Scheme 4 for the conversion of compounds of Formula (4) to compounds of Formula (7) (where Z is CR^2).

Compounds of Formula (1) may also be prepared from compounds of Formula (7) (where Y is O, S and Z is defined above) as outlined in Scheme 6:

SCHEME 6



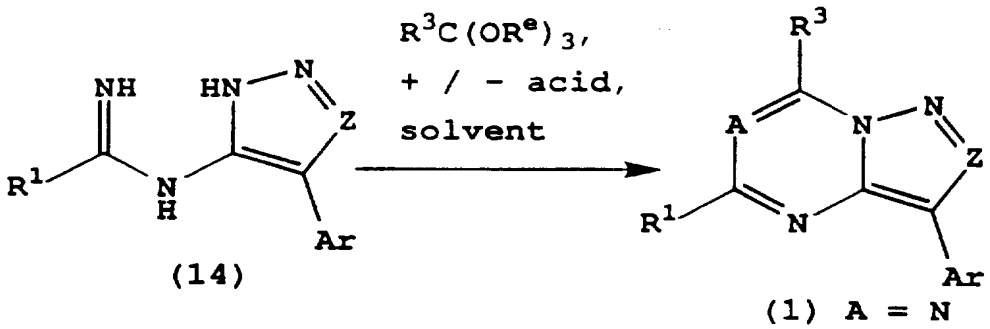
(7) Y = O, S; Z = N, CR^2 **(1) A = N**

Compounds of Formula (7) may be reacted with compounds of Formula R^3H in the presence of a dehydrating agent in an inert solvent at reaction temperatures ranging from 0°C to 250°C. Dehydrating agents include, but are not limited to, P_2O_5, molecular sieves or inorganic or organic acids. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Inert solvents may include, but are not limited to,

alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or halocarbons of 1 to 10 carbons and 1 to 10 halogens (preferably chloroform). Preferred reaction temperatures range from ambient temperature to 150°C.

Some compounds of Formula (1) (where A is N) may also be prepared by the methods shown in Scheme 7:

SCHEME 7

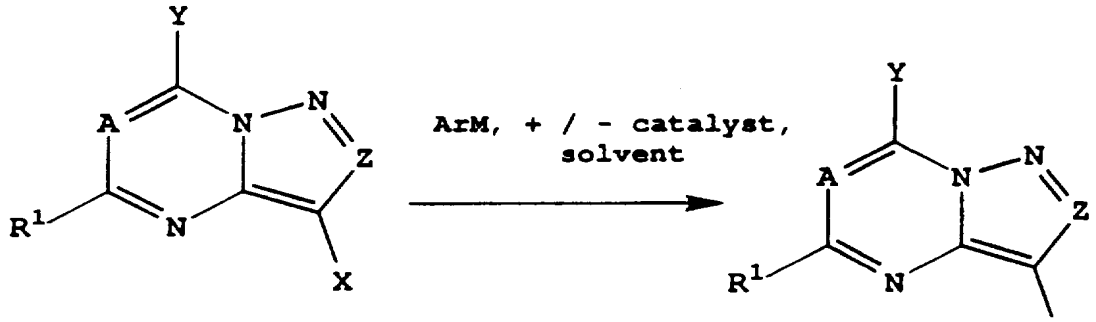


Intermediate compounds of Formula (14), where Z is defined above, may be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or

catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

Intermediate compounds of Formula (7) may also be synthesized by the reactions displayed in Scheme 8.

SCHEME 8



(15) Y = OH, SH NR^6R^7;
Z = N, CR^2,
X = Br, Cl, I, B(OR"")2

(7) A = N

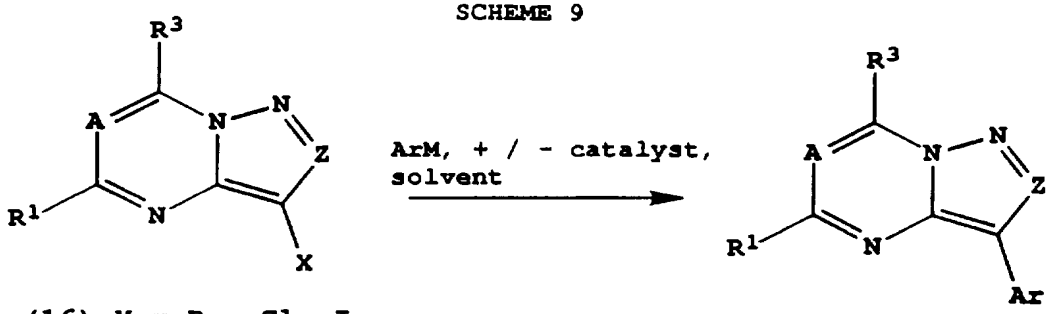
Compounds of Formula (15), (where Y is OH, SH, NR^6R^7; Z is defined above, X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an

organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ. Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$) or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

The choices of M and X are known to those skilled in the art (cf. Imamoto, T., Organocerium Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 231-250; Knochel, P., Organozinc, Organocadmium and Organomercury Reagents in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 1, 211-230; Knight, D.W., Coupling Reactions between sp^2 Carbon Centers, in Comprehensive Organic Synthesis, Trost, B.M. ed., (Elmsford, NY: Pergamon Press, 1991), 3, 481-520).

Compounds of Formula (1) may also be prepared using the methods shown in Scheme 9.

SCHEME 9



(16) X = Br, Cl, I, $B(OR"")_2$, O_3SCF_3

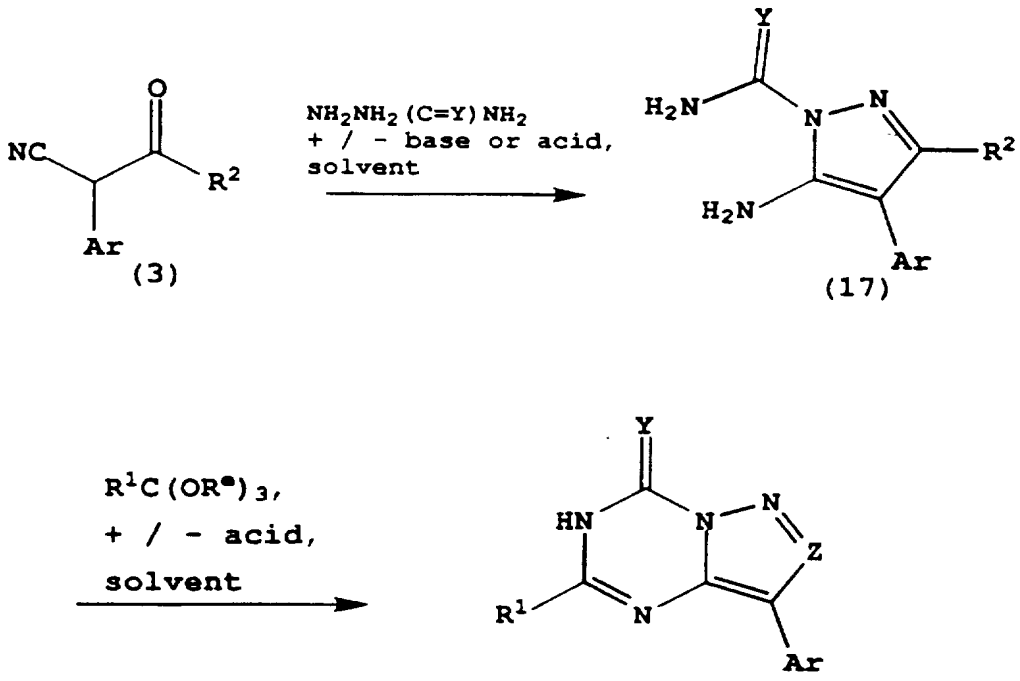
(1)

Compounds of Formula (16), where A, Z, R^1 and R^3 are defined above and X is Br, Cl, I, O_3SCF_3 or $B(OR"")_2$ and R"" is H or alkyl (1 to 6 carbons)) may be reacted with a compound of Formula ArM (where M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides) in the presence or absence of an organometallic catalyst in the presence or absence of a base in an inert solvents at temperatures ranging from -100°C to 200°C. Those skilled in the art will recognize that the reagents ArM may be generated in situ (see the above references in Comprehensive Organic Synthesis). Organometallic catalysts include, but are not limited to, palladium phosphine complexes (such as $Pd(PPh_3)_4$), palladium halides or alkanoates (such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$) or nickel complexes (such as $NiCl_2(PPh_3)_2$). Bases may include, but are not limited to, alkali metal carbonates or trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine). Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably

benzene or toluene) or water. Preferred reaction temperatures range from -80°C to 100°C.

Intermediate compounds of Formula (7) (where Y is O, S, NH, Z is CR^2 and R^1, R^2 and Ar are defined as above) may be prepared as illustrated in Scheme 10.

SCHEME 10



(7) Y = O, S, NH; Z = CR^2,

Compounds of Formula (3) may be reacted with compounds of Formula $H_2NNH(C=Y)NH_2$, where Y is O, S or NH, in the presence or absence of a base or acid in an inert solvent at temperatures from 0°C to 250°C to produce compounds of Formula (17). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts

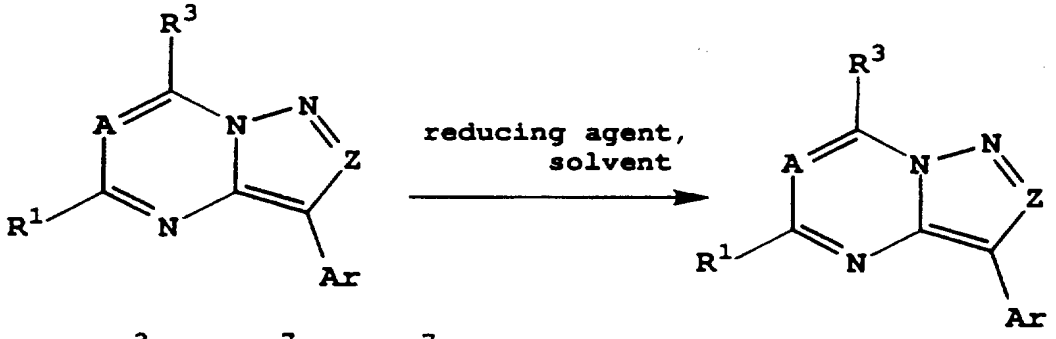
of such acids may be used. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane).

Preferred reaction temperatures range from 0°C to 150°C. Compounds of Formula (17) may then be reacted with compounds of Formula $R^3C(OR^e)3$, where R^e may be alkyl (1 to 6 carbons) in the presence or absence of an acid in an inert solvent at temperatures ranging from 0°C to 250°C. Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably

acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 50°C to 150°C.

In Scheme 11, the procedures which may be used to convert compounds of Formula (1), where R^3 is COR^7, CO_2R^7, NR^8COR^7 and $CONR^6R^7$, to other compounds of Formula (1), where R^3 is $CH(OH)R^7$, CH_2OH, $NR^8CH_2R^7$ and $CH_2NR^6R^7$ by treatment with a reducing agent in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 11



(1) $R^3 = COR^7$, CO_2R^7, $CONR^6R^7$

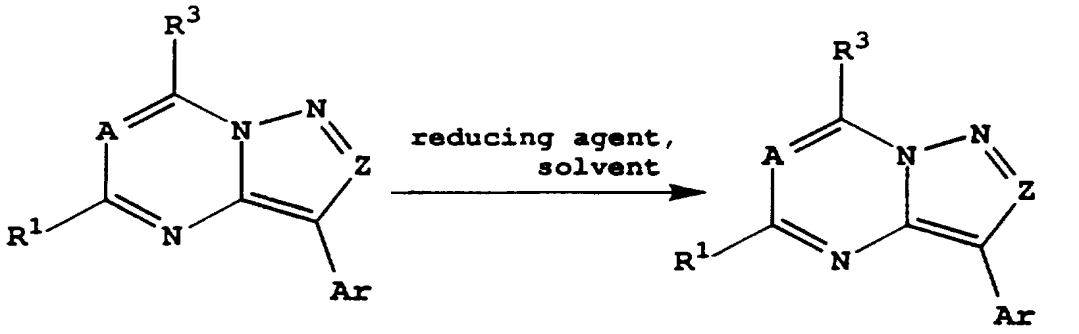
(1) $R^3 = C(OH)R^7$, CH_2OH, $CH_2NR^6R^7$

Reducing agents include, but are not limited to, alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides, or dialkyl aluminum

hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

In Scheme 12, the procedures are shown which may be used to convert compounds of Formula (1), where R^3 is COR^7 or CO_2R^7, to other compounds of Formula (1), where R^3 is $C(OH)(R^7)_2$ by treatment with a reagent of Formula R^7M in an inert solvent at temperatures ranging from -80°C to 250°C.

SCHEME 12

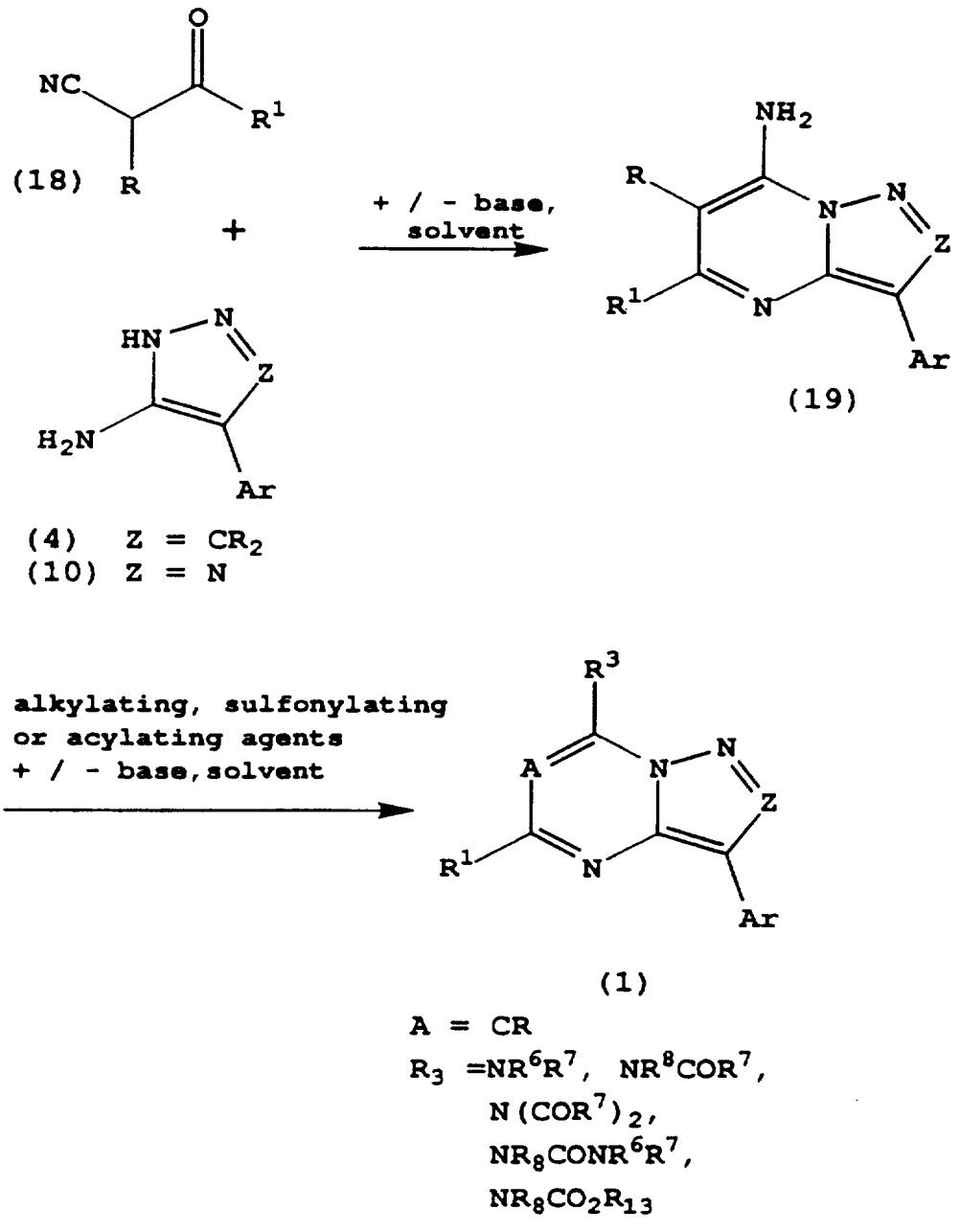


(1) $R^3 = COR^7$, CO_2R^7, (1) $R^3 = C(OH)(R^7)_2$

M is halogen, alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, $CeBr_2$ or copper halides. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$, may be synthesized as depicted in Scheme 13.

SCHEME 13



Reaction of compounds of Formula (18), where R and R^1 are defined above, with compounds of Formula (4) or (10) in the presence or absence of base in an inert solvent may produce compounds of Formula (19) at temperatures

ranging from -50°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

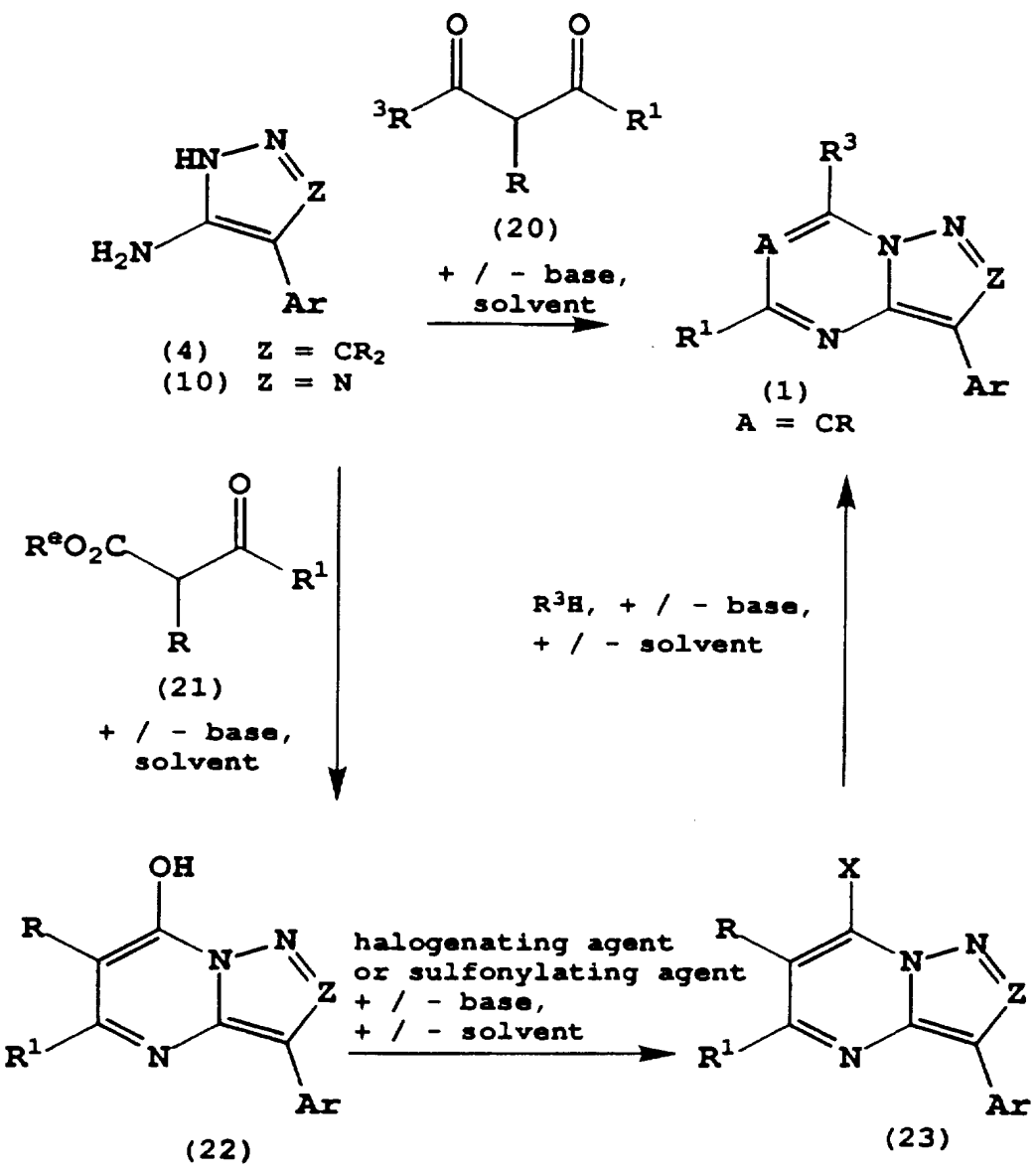
Compounds of Formula (19) may then be reacted with alkylating agents, sulfonylating agents or acylating agents or sequential reactions with combinations thereof, in the presence or absence of a base in an inert solvent at reaction temperatures ranging from -80°C to 250°C may afford compounds of Formula (1), where R^3 may be $-NR^8COR^7$, $-N(COR^7)_2$, $-NR^8CONR^6R^7$, $-NR^8CO_2R^{13}$, $-NR^6R^7$, $-NR^8SO_2R^7$. Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates; C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates; C_2-C_8 alkoxyalkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-

C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; aryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; heteroaryl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates; or heterocyclyl(C_1-C_4 alkyl)-halides, -tosylates, -mesylates or -triflates. Acylating agents may include, but are not limited to, C_1-C_{10} alkanoyl halides or anhydrides, C_1-C_{10} haloalkanoyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkanoyl halides or anhydrides, C_3-C_6 cycloalkanoyl halides or anhydrides, C_4-C_{12} cycloalkylalkanoyl halides or anhydrides, aroyl halides or anhydrides, aryl(C_1-C_4) alkanoyl halides or anhydrides, heteroaroyl halides or anhydrides, heteroaryl(C_1-C_4) alkanoyl halides or anhydrides, heterocyclylcarboxylic acid halides or anhydrides or heterocyclyl(C_1-C_4) alkanoyl halides or anhydrides. Sulfonylating agents include, but are not limited to, C_1-C_{10} alkylsulfonyl halides or anhydrides, C_1-C_{10} haloalkylsulfonyl halides or anhydrides with 1 - 10 halogens, C_2-C_8 alkoxyalkylsulfonyl halides or anhydrides, C_3-C_6 cycloalkylsulfonyl halides or anhydrides, C_4-C_{12} cycloalkylalkylsulfonyl halides or anhydrides, arylsulfonyl halides or anhydrides, aryl(C_1-C_4 alkyl)-, heteroarylsulfonyl halides or anhydrides, heteroaryl(C_1-C_4 alkyl)sulfonyl halides or anhydrides, heterocyclylsulfonyl halides or anhydrides or heterocyclyl(C_1-C_4 alkyl)sulfonyl halides or anhydrides. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably

pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (1), where A is CR and R is defined above, may be synthesized by the methods depicted in Scheme 14.

SCHEME 14



Compounds of Formula (4) or (10) may be treated with compounds of Formula (20), where R^1 and R^3 are defined above in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited

to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Alternatively, compounds of Formula (1) where A is CR and R is defined above, may be synthesized through intermediates (22) and (23).

Compounds of Formula (4) or (10) may be treated with compounds of Formula (21), where R^1 is defined above and R^e is alkyl (1 - 6 carbons), in the presence or absence of base in an inert solvent at temperatures ranging from 0°C to 250°C to give compounds of Formula (1), where A is CR and R is defined above. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C. Compounds of Formula (22) may be treated with a halogenating agent or sulfonylating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (23) (where X is halogen, alkanesulfonyloxy, arylsulfonyloxy or haloalkane-sulfonyloxy). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Sulfonylating agents include, but are not limited to, alkanesulfonyl halides or anhydrides (such as methanesulfonyl chloride or methanesulfonic acid anhydride), arylsulfonyl halides or anhydrides (such as p-toluenesulfonyl chloride or anhydride) or haloalkylsulfonyl halides or anhydrides (preferably trifluoromethanesulfonic anhydride). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

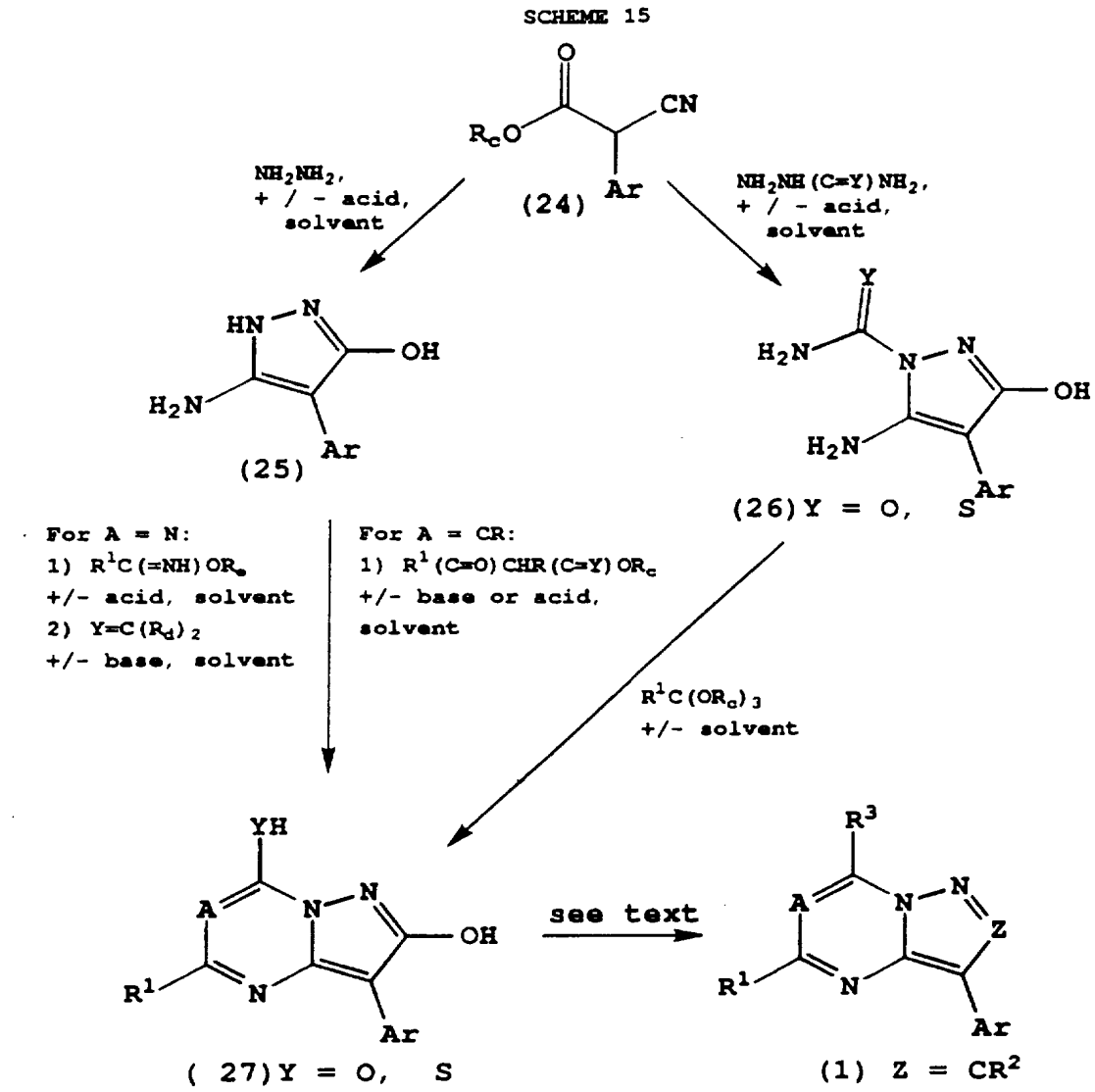
N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

Compounds of Formula (23) may be reacted with compounds of Formula R^3H (where R3 is defined as above except R^3 is not SH, COR^7, CO_2R^7, aryl or heteroaryl) in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate compounds of Formula (1). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

Some compounds of Formula (1) may also be prepared using the methods shown in Scheme 15.

SCHEME 15



A compound of Formula (24) (R_c is a lower alkyl group and Ar is defined as above) may be reacted with hydrazine in the presence or absence of an inert solvent to afford an intermediate of Formula (25), where Ar is defined as above. The conditions employed are similar to those used for the preparation of intermediate of Formula (4) from compound of Formula (3) in Scheme 4. Compounds of Formula (25), where A is N, may be reacted with reagents of the formula $R^1C(=NH)OR_e$, where R^1 is

defined above and R_e is a lower alkyl group) in the presence or absence of an acid in an inert solvent, followed by reaction with a compound of formula YisC(R_d)2 (where Y is O or S and R^d is halogen (preferably chlorine), alkoxy (1 to 4 carbons) or alkylthio (1 to 4 carbons)) in the presence or absence of a base in an inert solvent to give compounds of Formula (27) (where A is N and Y is O, S). The conditions for these transformations are the same as those employed for the conversions of compound of Formula (4) to compound of Formula (7) in Scheme 4.

Alternatively, compounds of Formula (25), where A is CR, may be reacted with compounds of the formula R^1(C=O)CHR(C=Y)OR_c (where R^1 and R are defined as above and R_c is a lower alkyl group) to give a compound of Formula (27) (where A is CR) using conditions similar to those employed for the conversion of compounds of Formula (21) to compounds of Formula (22) in Scheme 14. Intermediates of Formula (27) (where Y is O) may be treated with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H or R^2H in the presence or absence of a base in an inert solvent to give compounds of Formula (1) (where Z is CR^2).

It will be recognized by those skilled in the art that various combinations of halogenating agents, sulfonylating agents, R^3H or R^2H may be used in different orders of reaction sequences in Scheme 15 to afford compounds of Formula (1). For example, in some cases, it may be desirable to react compounds with stoichiometric amounts of halogenating agents or sulfonylating agents, react with R^2H (or R^3H), then repeat the reaction with halogenating agents or sulfonylating agents and react with R^3H (or R^2H) to give compounds of Formula (1). The reaction conditions and reagents used for these conversions are similar to the

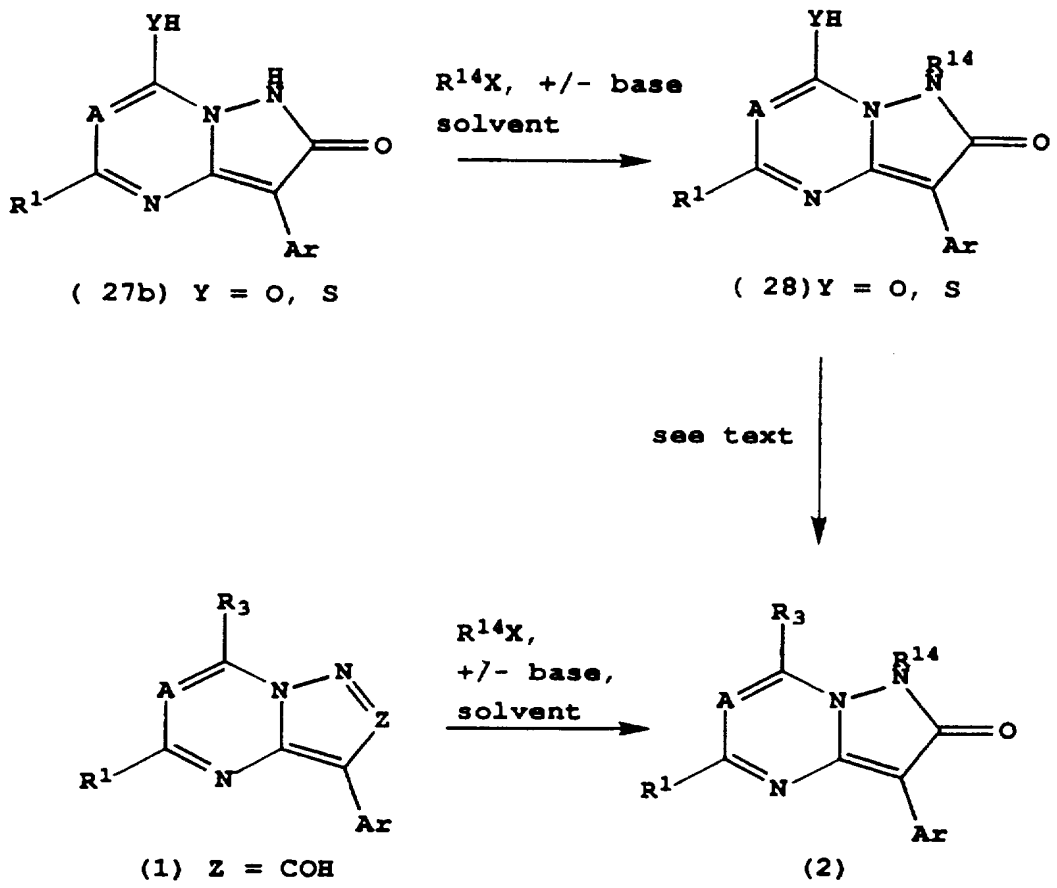
ones employed for the conversion of intermediate compounds of Formulae (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N).

Alternatively, compounds of Formula (27) (where Y is S) may be converted to compounds of Formula (1) in Scheme 15. Intermediate compounds of Formula (27) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1) may be prepared from compounds of Formula (24), using an alternate route as depicted in Scheme 15. Compounds of Formula (24) may be converted to compounds of Formula (27) via reaction with compounds of formula $NH_2NH(C=NH)NH_2$ in the presence or absence of an acid in an inert solvent, followed by reaction with compounds $R^1C(OR_c)_3$ (where R_c is lower alkyl and R^1 is defined as above), using the conditions employed for the conversion of compounds of Formulae (3) to (17) to (7) in Scheme 10.

Some compounds of Formula (2) may be prepared by the methods illustrated in Scheme 16.

SCHEME 16



Compounds of Formula (27b) may be treated with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures of Formula (28). Compounds of Formula (28) (Y is O) may then be converted to compounds of Formula (2) by treatment with halogenating agents or sulfonylating agents in the presence or absence of a base in an inert solvent, followed by reaction with R^3H in the presence or absence of a base in an inert solvent to give compounds of Formula (2). The reaction conditions used for these conversions are similar to the

ones employed for the conversion of intermediate compounds (22) to (23) to (1) in Scheme 14 (for A is CR) or the conversion of intermediate compounds of Formulae (7) to (8) to (1) in Scheme 1 (where A is N). Alternatively, compounds of Formula (28) (Y is S) may be alkylated with a compound R^fX (where R^f is lower alkyl and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in an inert solvent, (then optionally oxidized with an oxidizing agent in an inert solvent) and then reacted with R^3H in the presence or absence of a base in an inert solvent to give a compound of Formula (1). The conditions and reagents employed are similar to those used in the conversion of intermediate compounds of Formulae (7) to (12) (or to (13)) to compounds of Formula (1) in Scheme 2.

Compounds of Formula (1), where Z is COH, may be converted to compounds of Formula (2) as illustrated in Scheme 16. Treatment with various alkylating agents $R^{14}X$ (where R^{14} is defined above and X is halogen, alkanesulfonyloxy or haloalkanesulfonyloxy) in the presence or absence of a base in an inert solvent to afford structures (2). It will be recognized by one skilled in the art that the methods used in Scheme 16 may also be used to prepare compounds of Formula (1) where Z is COR^7.

For Scheme 16, the terms "base" and " inert solvent" may have the meanings given below. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents

may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 100°C.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an IBM-Bruker FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was

performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

EXAMPLE 1

Preparation of
2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]
-pyrazolo-[1,3,5]-triazin-4(3H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

A. 1-Cyano-1-(2,4-dimethylphenyl)propan-2-one

Sodium pellets (9.8g, 0.43 mol) were added portionwise to a solution of 2,4-dimethylphenylacetonitrile (48 g, 0.33 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to afford a white solid (45.7g, 74% yield): NMR ($CDCl_3$,300 MHz):; CI-MS: 188 (M + H).

B. 5-Amino-4-(2,4-dimethylphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2,4-dimethylphenyl)propan-2-one (43.8g, 0.23 mol), hydrazine-hydrate (22 mL, 0.46 mol), glacial acetic acid (45 mL, 0.78 mol) and toluene (500 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated ammonium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale brown viscous oil (34.6g, 75% yield): NMR ($CDCl_3$,300 MHz): 7.10 (s, 1H), 7.05 (d, 2H, J=1), 2.37 (s, 3H), 2.10 (s, 3H); CI-MS: 202 (M + H).

C. 5-Acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt

Ethyl acetamidate hydrochloride (60g, 0.48 mol) was added quickly to a rapidly stirred mixture of potassium carbonate (69.5g, 0.50 mol), dichloromethane (120 mL) and water (350 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 X 120 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed by simple distillation and the pot residue, a clear pale yellow liquid, (35.0 g) was used without further purification.

Glacial aetic acid (9.7 mL, 0.17 mol) was added to a stirred mixture of 5-amino-4-(2,4-dimethylphenyl)-3-methylpyrazole (34g, 0.17 mol), ethyl acetamidate (22g, 0.25 mol) and acetonitrile (500 mL). The resulting reaction mixture was stirred at room temperature for 3 days; at the end of which time, it was concentrated in vacuo to about one-third of its original volume. The resulting suspension was filtered and the collected

solid was washed with copious amounts of ether. The white solid was dried *in vacuo* (31.4g, 61% yield): NMR (DMSO-d_6,300 MHz): 7.00 (s, 1H), 6.90 (dd, 2H, J=7, 1), 2.28 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90 (s, 3H), 1.81 (s, 3H); CI-MS: 243 (M + H).

D. 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-[1,3,5]-triazin-4(3H)-one

Sodium pellets (23g, 1 mol) were added portionwise to ethanol (500 mL) with vigorous stirring. After all the sodium reacted, 5-acetamidino-4-(2,4-dimethylphenyl)-3-methylpyrazole, acetic acid salt (31.2g, 0.1 mol) and diethyl carbonate (97 mL, 0.8 mol) were added. The resulting reaction mixture was heated to reflux temperature and stirred for 18 hours. The mix was cooled to room temperature and solvent was removed in vacuo. The residue was dissolved in water and a 1N HCl solution was added slowly until pH = 5-6. The aqueous layer was extracted with ethyl acetate three times; the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a pale tan solid (26g, 98% yield): NMR ($CDCl_3$,300 MHz): 7.15(s, 1H), 7.09 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H); CI-MS: 269 (M + H).

EXAMPLE 2

Preparation of
5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(6H)-one
(Formula 7, where Y is O, R_1 is CH_3, Z is N, Ar is 2,4,6-trimethylphenyl)

A. 1-Phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole

A mixture of 2,4,6-trimethylbenzyl cyanide (1.0g, 6.3 mmol), benzyl azide (0.92g, 6.9 mmol) and potassium

t-butoxide (0.78g, 6.9 mmol) in tetrahydrofuran (10mL) was stirred at ambient temperature for 2.5 days. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a brown oil. Trituration with ether and filtration afforded a yellow solid (1.12g, 61% yield): NMR ($CDCl_3$,300 MHz):7.60-7.30 (m, 5H), 7.30-7.20 (m, 2H), 5.50 (s, 2H), 3.18 (br s, 2H), 2.30 (s, 3H), 2.10 (s, 6H); CI-MS: 293 (M + H).

B. 4-(2,4,6-Trimethylphenyl)-5-aminotriazole

Sodium (500 mg, 22 mmol) was added with stirring to a mixture of liquid ammonia (30 mL) and 1-phenylmethyl-4-(2,4,6-trimethylphenyl)-5-aminotriazole (1.1g, 3.8 mmol). The reaction mixture was stirred until a dark green color persisted. An ammonium chloride solution (mL) was added and the mixture was stirred while warming to ambient temperature over 16 hours. The residue was treated with a 1M HCl solution and filtered. The aqueous layer was basified with a concentrated ammonium hydroxide solution (pH = 9) and then extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give a yellow solid (520 mg), which was homogeneous by thin layer chromatography (ethyl acetate):
NMR ($CDCl_3$,300 MHz): 6.97 (s, 2H), 3.68-3.50 (br.s, 2H), 2.32 (s, 3H), 2.10 (s, 6H); CI-MS: 203 (M + H).

C. 4-(2,4,6-Trimethylphenyl)-5-acetamidinotriazole, acetic acid salt

A mixture of 4-(2,4,6-trimethylphenyl)-5-aminotriazole (400 mg, 1.98 mmol), ethyl acetamidate (261 mg, 3 mmol) and glacial acetic acid (0.1 mL, 1.98 mmol) in acetonitrile (6 mL) was stirred at ambient

temperature for 4 hours. The resulting suspension was filtered and the collected solid was washed with copious amounts of ether. Drying *in vacuo* afforded a white solid (490 mg, 82% yield): NMR (DMSO-d_6,300 MHz):7.90-7.70 (br s, 0.5H), 7.50-7.20 (br. s, 0.5H), 6.90 (s, 2H), 6.90 (s, 2H), 3.50-3.10 (br s, 3H), 2.30-2.20 (br s, 3H), 2.05 (d, 1H, J = 7), 1.96 (s, 6H), 1.87 (s, 6H); CI-MS: 244 (M + H).

D. 5-methyl-3-(2,4,6-trimethylphenyl)[1,5-a]-[1,2,3]-triazolo-[1,3,5]-triazin-7(4H)-one

Sodium (368 mg, 16.2 mmol) was added with stirring to ethanol (10 mL) at room temperature. After the sodium had reacted, 4-(2,4,6-trimethylphenyl)-5-acetamidino-triazole, acetic acid salt (490 mg, 1.6 mmol) and diethyl carbonate (1.6 mL, 13 mmol) were added. The reaction mixture was stirred at reflux temperature for 5 hours, then cooled to room temperature. The reaction mixture was diluted with water; a 1N HCl solution was added until pH = 5-6 and three extractions with ethyl acetate were performed. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a yellow residue. Trituration with ether and filtration afforded a yellow solid (300 mg, 69% yield): NMR ($CDCl_3$,300 MHz): 6.98 (s, 2H), 2.55 (s, 3H), 2.35 (s, 3H), 2.10 (s, 6H); CI-MS: 270 (M + H).

EXAMPLE 3

Preparation of 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $CH(CHCO_2CH_3)_2$, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed *in vacuo*. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed in vacuo to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

B. 4-(di(carbomethoxy)methyl)-2,7-dimethyl-8-(2,4-dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine

Sodium hydride (60% in oil, 80 mg, 2 mmol) was washed with hexanes twice, decanted after each washing and taken up in anhydrous tetrahydrofuran (THF, 1 mL). A solution of diethyl malonate (0.32g, 2 mmol) in THF (2 mL) was added dropwise over 5 min, during which time vigorous gas evolution ensued. A solution of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolotriazine (0.5g, 1.75 mmol) in THF (2 mL) was added and the reaction mixture was then stirred under a nitrogen atmosphere for 48 hours. The resulting suspension was poured onto water and extracted three times with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown

oil. Column chromatography (ethyl acetate:hexanes::1:9) afforded, after removal of solvent *in vacuo*, a pale yellow solid (Rf = 0.2, 250 mg, 35% yield): mp 50-52°C; NMR ($CDCl_3$, 300 MHz): 12.35 (br.s, 1H, 7.15-7.00 (m, 3H), 4.40 (q, 2H, J = 7), 4.30 (q, 2H, J = 7), 2.4, 2.35, 2.3, 2.2, 2.1 (5 s, 12H), 1.4 (t, 3H, J = 7), 1.35-1.25 (m, 3H); CI-HRMS: Calcd: 411.2032, Found: 411.2023.

EXAMPLE 6

Preparation of 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

(Formula 1, where R^3 is $NHCH(CH_2OCH_3)_2$, R_1 is CH_3, Z is $C-CH_3$, Ar is 2,4-dichlorophenyl)

A. 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]- pyrazolotriazine

A mixture of 2,7-dimethyl-8-(2,4 dimethylphenyl)[1,5-a]-pyrazolo-1,3,5-triazin-4-one (Example 1, 1.38g, 4.5 mmol), N,N-dimethylaniline (1 mL, 8 mmol) and phosphorus oxychloride (10 mL) was stirred at reflux temperature for 48 hours. The excess phosphorus oxychloride was removed in vacuo. The residue was poured onto ice-water, stirred briefly and extracted quickly with ethyl acetate three times. The combined organic layers were washed with ice water, then dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a brown oil. Flash column chromatography (ethyl acetate:hexanes::1:4) gave one fraction (Rf = 0.5) Solvent was removed *in vacuo* to afford a yellow oil (1.0g, 68% yield): NMR ($CDCl_3$,300 MHz): 7.55 (d, 1H, J = 1), 7.38 (dd, 1H, J = 7,1), 7.30 (d, 1H, J = 7), 2.68 (s, 3H), 2.45 (s, 3H); CI-MS: 327 (M + H).

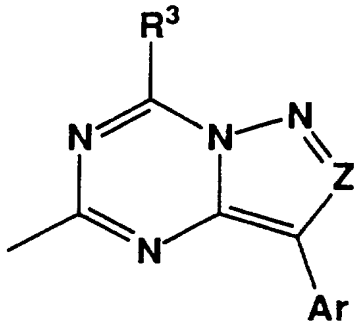
B. 4-(1,3-dimethoxy-2-propylamino)-2,7-dimethyl-8-(2,4- dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine

A mixture of 4-chloro-2,7-dimethyl-8-(2,4-dichlorophenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Part A, 570 mg, 1.74 mmol), 1,3-dimethoxypropyl-2-aminopropane (25mg, 2.08 mmol) and ethanol (10 mL) was stirred at ambient temperature for 18 hours. The reaction mixture was poured onto water (25 mL) and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo*. Column chromatography (CH_2Cl_2:CH_3OH::50:1) afforded one fraction. Removal of solvent *in vacuo* gave a solid (250 mg, 35% yield): mp 118-120°C; NMR ($CDCl_3$,300 MHz): 7.50 (s, 1H), 7.28 (dd, 2H, J = 8,1), 6.75 (d, 1H, J = 8), 4.70-4.58 (m, 1H), 3.70-3.55 (m, 4H), 3.43 (s, 6H), 2.50 (s, 3H), 2.35 (s, 3H); CI-HRMS: Calcd: 409.1072, Found: 409.1085; Analysis Calcd. for $C_{18}H_{21}Cl_2N_5O_2$: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following additional examples of Tables 1-4 may be prepared.

The examples delineated in TABLE 1 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 1



Ex.	Z	B_3	Ar	mp(°C)
6[a]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	118-120
7[b]	C-Me	$NHCHPr_2$	2,4-Cl_2-Ph	114-116
8[c]	C-Me	NEtBu	2,4-Cl_2-Ph	oil
9[d]	C-Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph	oil
10[e]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph	oil
11[f]	C-Me	NH-3-heptyl	2,4-Cl_2-Ph	90-92
12[g]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph	179-181
13[h]	C-Me	NEt_2	2,4-Cl_2-Ph	133-134
14[i]	C-Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph	oil
15[j]	C-Me	NH-3-pentyl	2,4-Cl_2-Ph	139-140
16[k]	C-Me	NMePh	2,4-Cl_2-Ph	60-62
17[l]	C-Me	NPr_2	2,4-Cl_2-Ph	oil
18[m]	C-Me	NH-3-hexyl	2,4-Cl_2-Ph	130-132
19	C-Me	morpholino	2,4-Cl_2-Ph	
20	C-Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Cl_2-Ph	
21	C-Me	$NHCH(CH_2Ph)CH_2OMe$	2,4-Cl_2-Ph	
22	C-Me	NH-4-tetrahydropyranyl	2,4-Cl_2-Ph	
23	C-Me	NH-cyclopentyl	2,4-Cl_2-Ph	
24	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Cl_2-Ph	
25	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Cl_2-Ph	
26[n]	C-Me	OEt	2,4-Cl_2-Ph	141-143
27	C-Me	$OCH(Et)CH_2OMe$	2,4-Cl_2-Ph	

	28	C-Me	OCH_2Ph	2,4-Cl_2-Ph	
	29	C-Me	O-3-pentyl	2,4-Cl_2-Ph	
	30	C-Me	SEt	2,4-Cl_2-Ph	
	31	C-Me	S(O)Et	2,4-Cl_2-Ph	
5	32	C-Me	SO_2Et	2,4-Cl_2-Ph	
	33	C-Me	$CH(CO_2Et)_2$	2,4-Cl_2-Ph	
	34	C-Me	$C(Et)(CO_2Et)_2$	2,4-Cl_2-Ph	
	35	C-Me	$CH(Et)CH_2OH$	2,4-Cl_2-Ph	
	36	C-Me	$CH(Et)CH_2OMe$	2,4-Cl_2-Ph	
10	37	C-Me	$CONMe_2$	2,4-Cl_2-Ph	
	38	C-Me	$COCH_3$	2,4-Cl_2-Ph	
	39	C-Me	$CH(OH)CH_3$	2,4-Cl_2-Ph	
	40	C-Me	C(OH)Ph-3-pyridyl	2,4-Cl_2-Ph	
	41	C-Me	Ph	2,4-Cl_2-Ph	
15	42	C-Me	2-CF_3-Ph	2,4-Cl_2-Ph	
	43	C-Me	2-Ph-Ph	2,4-Cl_2-Ph	
	44	C-Me	3-pentyl	2,4-Cl_2-Ph	
	45	C-Me	cyclobutyl	2,4-Cl_2-Ph	
	46	C-Me	3-pyridyl	2,4-Cl_2-Ph	
20	47	C-Me	$CH(Et)CH_2CONMe_2$	2,4-Cl_2-Ph	
	48	C-Me	$CH(Et)CH_2CH_2NMe_2$	2,4-Cl_2-Ph	
	49[o]	C-Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph	125-127
	50	C-Me	$NHCHPr_2$	2,4,6-Me_3-Ph	
	51	C-Me	NEtBu	2,4,6-Me_3-Ph	
25	52	C-Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4,6-Me_3-Ph	
	53[ae]	C-Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph	123-124
	54	C-Me	NH-3-heptyl	2,4,6-Me_3-Ph	
	55[ac]	C-Me	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph	145-146
	56[ah]	C-Me	NEt_2	2,4,6-Me_3-Ph	88-90
30	57[ai]	C-Me	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph	132-134
	58[ad]	C-Me	NH-3-pentyl	2,4,6-Me_3-Ph	134-135
	59	C-Me	NMePh	2,4,6-Me_3-Ph	
	60	C-Me	NPr_2	2,4,6-Me_3-Ph	
	61	C-Me	NH-3-hexyl	2,4,6-Me_3-Ph	
35	62	C-Me	morpholino	2,4,6-Me_3-Ph	
	63	C-Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph	

	64	C-Me	$NHCH(CH_2Ph)CH_2OMe$	$2,4,6-Me_3-Ph$	
	65	C-Me	NH-4-tetrahydropyranyl	$2,4,6-Me_3-Ph$	
	66	C-Me	NH-cyclopentyl	$2,4,6-Me_3-Ph$	
	67	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	$2,4,6-Me_3-Ph$	
	68	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	$2,4,6-Me_3-Ph$	
	69	C-Me	OEt	$2,4,6-Me_3-Ph$	
	70	C-Me	$OCH(Et)CH_2OMe$	$2,4,6-Me_3-Ph$	
	71	C-Me	OCH_2Ph	$2,4,6-Me_3-Ph$	
	72	C-Me	O-3-pentyl	$2,4,6-Me_3-Ph$	
	73	C-Me	SEt	$2,4,6-Me_3-Ph$	
	74	C-Me	S(O)Et	$2,4,6-Me_3-Ph$	
	75	C-Me	SO_2Et	$2,4,6-Me_3-Ph$	
	76	C-Me	$CH(CO_2Et)_2$	$2,4,6-Me_3-Ph$	
	77	C-Me	$C(Et)(CO_2Et)_2$	$2,4,6-Me_3-Ph$	
	78	C-Me	$CH(Et)CH_2OH$	$2,4,6-Me_3-Ph$	
	79	C-Me	$CH(Et)CH_2OMe$	$2,4,6-Me_3-Ph$	
	80	C-Me	$CONMe_2$	$2,4,6-Me_3-Ph$	
	81	C-Me	$COCH_3$	$2,4,6-Me_3-Ph$	
	82	C-Me	$CH(OH)CH_3$	$2,4,6-Me_3-Ph$	
	83	C-Me	C(OH)Ph-3-pyridyl	$2,4,6-Me_3-Ph$	
	84	C-Me	Ph	$2,4,6-Me_3-Ph$	
	85	C-Me	$2-CF_3-Ph$	$2,4,6-Me_3-Ph$	
	86	C-Me	2-Ph-Ph	$2,4,6-Me_3-Ph$	
	87	C-Me	3-pentyl	$2,4,6-Me_3-Ph$	
	88	C-Me	cyclobutyl	$2,4,6-Me_3-Ph$	
	89	C-Me	3-pyridyl	$2,4,6-Me_3-Ph$	
	90	C-Me	$CH(Et)CH_2CONMe_2$	$2,4,6-Me_3-Ph$	
	91	C-Me	$CH(Et)CH_2CH_2NMe_2$	$2,4,6-Me_3-Ph$	
	92[p]	C-Me	$NHCH(CH_2OMe)_2$	$2,4-Me_2-Ph$	44-45
	93[q]	C-Me	$N(CH_2CH_2OMe)_2$	$2,4-Me_2-Ph$	oil
	94[r]	C-Me	$NHCH(Et)CH_2OMe$	$2,4-Me_2-Ph$	102-104
	95[s]	C-Me	NH-3-pentyl	$2,4-Me_2-Ph$	102-104
	96[t]	C-Me	NEt_2	$2,4-Me_2-Ph$	oil
	97[u]	C-Me	$N(CH_2CN)_2$	$2,4-Me_2-Ph$	148-150

	98[v]	C-Me	NHCH(Me)CH_2OMe	2,4-Me_2-Ph	102-104
	99[w]	C-Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph	oil
	100[x]	C-Me	NPr-c-C_3H_5	2,4-Me_2-Ph	oil
	101[y]	C-Me	NHCH(Me)CH_2NMe_2	2,4-Me_2-Ph	47-48
5	102[z]	C-Me	N(c-C_3H_5)CH_2CH_2CN	2,4-Me_2-Ph	117-118
	103[aa]	C-Me	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph	oil
	104[ab]	C-Me	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph	oil
	105	C-Me	$NHCHPr_2$	2,4-Me_2-Ph	
	106	C-Me	NEtBu	2,4-Me_2-Ph	
10	107	C-Me	NPr(CH_2-c-C_3H_5)	2,4-Me_2-Ph	
	108	C-Me	NH-3-heptyl	2,4-Me_2-Ph	
	109	C-Me	NEt_2	2,4-Me_2-Ph	
	110	C-Me	NHCH(CH_2OEt)$_2$	2,4-Me_2-Ph	
	111	C-Me	NH-3-pentyl	2,4-Me_2-Ph	
15	112	C-Me	NMePh	2,4-Me_2-Ph	
	113	C-Me	NPr_2	2,4-Me_2-Ph	
	114	C-Me	NH-3-hexyl	2,4-Me_2-Ph	
	115	C-Me	morpholino	2,4-Me_2-Ph	
	116	C-Me	N(CH_2Ph)CH_2CH_2OMe	2,4-Me_2-Ph	
20	117	C-Me	NHCH(CH_2Ph)CH_2OMe	2,4-Me_2-Ph	
	118	C-Me	NH-4-tetrahydropyranyl	2,4-Me_2-Ph	
	119	C-Me	NH-cyclopentyl	2,4-Me_2-Ph	
	120	C-Me	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Me_2-Ph	
25	121	C-Me	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Me_2-Ph	
	122	C-Me	OEt	2,4-Me_2-Ph	
	123	C-Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph	
	124	C-Me	OCH_2Ph	2,4-Me_2-Ph	
30	125	C-Me	O-3-pentyl	2,4-Me_2-Ph	
	126	C-Me	SEt	2,4-Me_2-Ph	
	127	C-Me	S(O)Et	2,4-Me_2-Ph	
	128	C-Me	SO_2Et	2,4-Me_2-Ph	
	3	C-Me	CH(CO_2Et)$_2$	2,4-Me_2-Ph	50-52
35	129	C-Me	C(Et)(CO_2Et)$_2$	2,4-Me_2-Ph	

	130	C-Me	CH(Et)CH_2OH	2,4-Me_2-Ph	
	131	C-Me	CH(Et)CH_2OMe	2,4-Me_2-Ph	
	132	C-Me	CH(Et)CH_2OEt	2,4-Me_2-Ph	
	133	C-Me	$CONMe_2$	2,4-Me_2-Ph	
5	134	C-Me	$COCH_3$	2,4-Me_2-Ph	
	135	C-Me	CH(OH)CH_3	2,4-Me_2-Ph	
	136	C-Me	C(OH)Ph-3-pyridyl	2,4-Me_2-Ph	
	137	C-Me	Ph	2,4-Me_2-Ph	
	138	C-Me	2-CF_3-Ph	2,4-Me_2-Ph	
10	139	C-Me	2-Ph-Ph	2,4-Me_2-Ph	
	140	C-Me	3-pentyl	2,4-Me_2-Ph	
	141	C-Me	cyclobutyl	2,4-Me_2-Ph	
	142	C-Me	3-pyridyl	2,4-Me_2-Ph	
	143	C-Me	CH(Et)CH_2CONMe_2	2,4-Me_2-Ph	
15	144	C-Me	CH(Et)$CH_2CH_2NMe_2$	2,4-Me_2-Ph	
	145[bc]	C-Me	NHCH(CH_2OMe)$_2$	2-Me-4-MeO-Ph	45-46
	146[bd]	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4-MeO-Ph	oil
	147[be]	C-Me	NHCH(Et)CH_2OMe	2-Me-4-MeO-Ph	86-88
	148[bf]	C-Me	N(Pr)CH_2CH_2CN	2-Me-4-MeO-Ph	oil
20	149	C-Me	OCH(Et)CH_2OMe	2-Me-4-MeO-Ph	
	150[af]	C-Me	NHCH(CH_2OMe)$_2$	2-Br-4-MeO-Ph	88-90
	151[al]	C-Me	N(CH_2CH_2OMe)$_2$	2-Br-4-MeO-Ph	oil
	152[ag]	C-Me	NHCH(Et)CH_2OMe	2-Br-4-MeO-Ph	95-97
	153	C-Me	N(Pr)CH_2CH_2CN	2-Br-4-MeO-Ph	
25	154	C-Me	OCH(Et)CH_2OMe	2-Br-4-MeO-Ph	
	155	C-Me	NHCH(CH_2OMe)$_2$	2-Me-4-NMe_2-Ph	
	156	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4-NMe_2-Ph	oil
	157	C-Me	NHCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph	
	158	C-Me	N(Pr)CH_2CH_2CN	2-Me-4-NMe_2-Ph	
30	159	C-Me	OCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph	
	160	C-Me	NHCH(CH_2OMe)$_2$	2-Br-4-NMe_2-Ph	
	161	C-Me	N(CH_2CH_2OMe)$_2$	2-Br-4-NMe_2-Ph	
	162	C-Me	NHCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph	
	163	C-Me	N(Pr)CH_2CH_2CN	2-Br-4-NMe_2-Ph	
35	164	C-Me	OCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph	
	165	C-Me	NHCH(CH_2OMe)$_2$	2-Br-4-i-Pr-Ph	

	166	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-i-Pr-Ph	
	167	C-Me	$NHCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph	
	168	C-Me	$N(Pr)CH_2CH_2CN$	2-Br-4-i-Pr-Ph	
	169	C-Me	$OCH(Et)CH_2OMe$	2-Br-4-i-Pr-Ph	
5	170	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-Me-Ph	
	171	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-Me-Ph	
	172	C-Me	$NHCH(Et)CH_2OMe$	2-Br-4-Me-Ph	
	173	C-Me	$N(Pr)CH_2CH_2CN$	2-Br-4-Me-Ph	
	174	C-Me	$OCH(Et)CH_2OMe$	2-Br-4-Me-Ph	
10	175[ar]	C-Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph	108-109
	176	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph	
	177	C-Me	$NHCH(Et)CH_2OMe$	2-Me-4-Br-Ph	
	178	C-Me	$N(Pr)CH_2CH_2CN$	2-Me-4-Br-Ph	
	179	C-Me	$OCH(Et)CH_2OMe$	2-Me-4-Br-Ph	
15	180	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph	
	181	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph	
	182	C-Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph	
	183	C-Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph	
	184	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
20	185	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
	186	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph	
	187	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph	
	188	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph	
	189	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph	
25	190	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph	
	191	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph	
	192	C-Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph	
	193	C-Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph	
	194	C-Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph	
30	195	C-Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph	
	196	C-Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl	
	197	C-Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl	
	198	C-Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph	
	199	C-Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph	
35	200	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	
	201	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph	

202	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
203	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
204	C-Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
205	C-Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
206	C-Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
207	C-Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
208	C-Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
209	C-Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
210	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
211	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
212	C-Me	$NHCH(CH_2OMe)_2$	2,4-[SMe]2-Ph
213	C-Me	$N(CH_2CH_2OMe)_2$	2,4-[SMe]2-Ph
214	C-Me	$NHCH(CH_2OMe)_2$	2,4-[SO_2Me]2-Ph
215	C-Me	$N(CH_2CH_2OMe)_2$	2,4-[SO_2Me]2-Ph
216	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
217	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
218	C-Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
219	C-Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
220	C-Me	$NHCH(CH_2OMe)_2$	2-$N(Me)_2$-4-Me-Ph
221	C-Me	$N(CH_2CH_2OMe)_2$	2-$N(Me)_2$-4-Me-Ph
222	C-Me	$NHCH(CH_2OMe)_2$	2-MeS-4,6-$(Me)_2$-Ph
223	C-Me	$N(CH_2CH_2OMe)_2$	2-MeS-4,6-$(Me)_2$-Ph
224	C-Me	$NHCH(CH_2OMe)_2$	2-(CH_3CO)-4,6-$(Me)_2$-Ph
225	C-Me	$N(CH_2CH_2OMe)_2$	2-(CH_3CO)-4,6-$(Me)_2$-Ph
226	H	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
227	H	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
228	CF3	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
229	CF3	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
230	N	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph
231	N	$NHCHPr_2$	2,4,6-Me_3-Ph
232	N	NEtBu	2,4,6-Me_3-Ph
233	N	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4,6-Me_3-Ph
234	N	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph
235	N	NH-3-heptyl	2,4,6-Me_3-Ph
236	N	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
237	N	NEt_2	2,4,6-Me_3-Ph

	238	N	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph
	239	N	NH-3-pentyl	2,4,6-Me_3-Ph
	240	N	NMePh	2,4,6-Me_3-Ph
	241	N	NPr_2	2,4,6-Me_3-Ph
5	242	N	NH-3-hexyl	2,4,6-Me_3-Ph
	243	N	morpholino	2,4,6-Me_3-Ph
	244	N	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph
	245	N	$NHCH(CH_2Ph)CH_2OMe$	2,4,6-Me_3-Ph
	246	N	NH-4-tetrahydropyranyl	2,4,6-Me_3-Ph
10	247	N	NH-cyclopentyl	2,4,6-Me_3-Ph
	248	N	1,2,3,4-tetrahydro-isoquinolinyl	2,4,6-Me_3-Ph
	249	N	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4,6-Me_3-Ph
15	250	N	OEt	2,4,6-Me_3-Ph
	251	N	$OCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
	252	N	OCH_2Ph	2,4,6-Me_3-Ph
	253	N	O-3-pentyl	2,4,6-Me_3-Ph
	254	N	SEt	2,4,6-Me_3-Ph
20	255	N	S(O)Et	2,4,6-Me_3-Ph
	256	N	SO_2Et	2,4,6-Me_3-Ph
	257	N	$CH(CO_2Et)_2$	2,4,6-Me_3-Ph
	258	N	$C(Et)(CO_2Et)_2$	2,4,6-Me_3-Ph
	259	N	$CH(Et)CH_2OH$	2,4,6-Me_3-Ph
25	260	N	$CH(Et)CH_2OMe$	2,4,6-Me_3-Ph
	261	N	$CONMe_2$	2,4,6-Me_3-Ph
	262	N	$COCH_3$	2,4,6-Me_3-Ph
	263	N	$CH(OH)CH_3$	2,4,6-Me_3-Ph
	264	N	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
30	265	N	Ph	2,4,6-Me_3-Ph
	266	N	2-CF_3-Ph	2,4,6-Me_3-Ph
	267	N	2-Ph-Ph	2,4,6-Me_3-Ph
	268	N	3-pentyl	2,4,6-Me_3-Ph
	269	N	cyclobutyl	2,4,6-Me_3-Ph
35	270	N	3-pyridyl	2,4,6-Me_3-Ph
	271	N	$CH(Et)CH_2CONMe_2$	2,4,6-Me_3-Ph

	272	N	$CH(Et)CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
	273	N	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
	274	N	$NHCHPr_2$	2,4-Me_2-Ph
	275	N	NEtBu	2,4-Me_2-Ph
	276	N	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Me_2-Ph
	277	N	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
	278	N	NH-3-heptyl	2,4-Me_2-Ph
	279	N	$NHCH(Et)CH_2OMe$	2,4-Me_2-Ph
	280	N	NEt_2	2,4-Me_2-Ph
	281	N	$NHCH(CH_2OEt)_2$	2,4-Me_2-Ph
	282	N	NH-3-pentyl	2,4-Me_2-Ph
	283	N	NMePh	2,4-Me_2-Ph
	284	N	NPr_2	2,4-Me_2-Ph
	285	N	NH-3-hexyl	2,4-Me_2-Ph
	286	N	morpholino	2,4-Me_2-Ph
	287	N	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Me_2-Ph
	288	N	$NHCH(CH_2Ph)CH_2OMe$	2,4-Me_2-Ph
	289	N	NH-4-tetrahydropyranyl	2,4-Me_2-Ph
	290	N	NH-cyclopentyl	2,4-Me_2-Ph
	291	N	1,2,3,4-tetrahydro-isoquinolinyl	2,4-Me_2-Ph
	292	N	CH_2-(1,2,3,4-tetrahydro-isoquinolinyl)	2,4-Me_2-Ph
	293	N	OEt	2,4-Me_2-Ph
	294	N	$OCH(Et)CH_2OMe$	2,4-Me_2-Ph
	295	N	OCH_2Ph	2,4-Me_2-Ph
	296	N	O-3-pentyl	2,4-Me_2-Ph
	297	N	SEt	2,4-Me_2-Ph
	298	N	S(O)Et	2,4-Me_2-Ph
	299	N	SO_2Et	2,4-Me_2-Ph
	300	N	$CH(CO_2Et)_2$	2,4-Me_2-Ph
	301	N	$C(Et)(CO_2Et)_2$	2,4-Me_2-Ph
	302	N	$CH(Et)CH_2OH$	2,4-Me_2-Ph
	303	N	$CH(Et)CH_2OMe$	2,4-Me_2-Ph
	304	N	$CONMe_2$	2,4-Me_2-Ph
	305	N	$COCH_3$	2,4-Me_2-Ph

	306	N	$CH(OH)CH_3$	$2,4\text{-}Me_2\text{-}Ph$	
	307	N	$C(OH)Ph\text{-}3\text{-}pyridyl$	$2,4\text{-}Me_2\text{-}Ph$	
	308	N	Ph	$2,4\text{-}Me_2\text{-}Ph$	
	309	N	$2\text{-}CF_3\text{-}Ph$	$2,4\text{-}Me_2\text{-}Ph$	
	310	N	2-Ph-Ph	$2,4\text{-}Me_2\text{-}Ph$	
	311	N	3-pentyl	$2,4\text{-}Me_2\text{-}Ph$	
	312	N	cyclobutyl	$2,4\text{-}Me_2\text{-}Ph$	
	313	N	3-pyridyl	$2,4\text{-}Me_2\text{-}Ph$	
	314	N	$CH(Et)CH_2CONMe_2$	$2,4\text{-}Me_2\text{-}Ph$	
	315	N	$CH(Et)CH_2CH_2NMe_2$	$2,4\text{-}Me_2\text{-}Ph$	
	316[an]	C-Me	NEt_2	2-Br-4-MeO-Ph	oil
	317[am]	C-Me	NH-3-pentyl	2-Br-4-MeO-Ph	oil
	318[aj]	C-Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$	101-103
	319[ao]	C-Me	$NH(c\text{-}C_3H_5)$	$2,4\text{-}Me_2\text{-}Ph$	oil
	320[ak]	C-Me	morpholino	$2,4,6\text{-}Me_3\text{-}Ph$	139-141
	321[ap]	C-Me	$NHCH(CH_2OMe)_2$	2-CN-4-Me-Ph	152-153
	322[aq]	C-Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	$2,4,6\text{-}Me_3\text{-}Ph$	149-151
	324[as]	C-Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-Br-Ph	115-117
	325[at]	C-Me	$NHCH(CH_2OMe)_2$	$2,5\text{-}Me_2\text{-}4\text{-}MeO\text{-}Ph$	55-57
	326[au]	C-Me	$N(CH_2CH_2OMe)_2$	$2,5\text{-}Me_2\text{-}4\text{-}MeO\text{-}Ph$	72
	327[av]	C-Me	NH-3-pentyl	$2,5\text{-}Me_2\text{-}4\text{-}MeO\text{-}Ph$	45-47
	328[aw]	C-Me	NEt_2	$2,5\text{-}Me_2\text{-}4\text{-}MeO\text{-}Ph$	oil
	329[ax]	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MePh	80-81
	330[ay]	C-Me	$NCH(Et)CH_2OMe$	2-Cl-4-MePh	77-79
	331[az]	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh	oil
	332[ba]	C-Me	$(S)\text{-}NHCH(CH_2CH_2OMe)CH_2OMe$	2-Cl-4-MePh	139-140
	333[bb]	C-Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	$2,5\text{-}Me_2\text{-}4\text{-}MeOPh$	120-122
	334[bg]	C-Me	NEt_2	2-Me-4-MeOPh	oil
	335[bh]	C-Me	OEt	2-Me-4-MeOPh	oil
	336[bi]	C-Me	$(S)\text{-}NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-MeOPh	oil
	337[bj]	C-Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2-Me-4-MeOPh	129
	338[bk]	C-Me	$NHCH(CH_2CH_2OEt)_2$	2-Me-4-MeOPh	amorph.
	339	C-Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	$2,4\text{-}Cl_2\text{-}Ph$	109-110
	340	C-Me	$(S)\text{-}NHCH(CH_2CH_2OMe)CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$	93-94
	341	C-Me	NH-3-pentyl	2-Me-4-BrPh	118-119
	342	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-BrPh	oil

	343	C-Me	NHCH(CH_2-iPr)CH_2OMe	2,4-Me_2-Ph	oil
	344	C-Me	NHCH(Pr)CH_2OMe	2,4-Me_2-Ph	94-95
	345	C-Me	NHCH(Et)CH_2OEt	2,4-Me_2-Ph	76-77
	346	C-Me	NHCH(CH_2OMe)CH_2CH_2OMe	2-Me-4-Me_2NPh	oil
5	347	C-Me	NEt_2	2-Me-4-ClPh	oil
	348	C-Me	NH-3-pentyl	2-Me-4-ClPh	122-124
	349	C-Me	N(CH_2CH_2OMe)$_2$	2-Me-4-ClPh	oil
	350	C-Me	NHCH(CH_2OMe)$_2$	2-Me-4-ClPh	122-123
	351	C-Me	NEt_2	2-Me-4-ClPh	oil
10	352	C-Me	NEt_2	2-Cl-4-MePh	oil
	353	C-Me	NH-3-pentyl	2-Cl-4-MePh	120-121
	354	C-Me	NHCH(CH_2OMe)$_2$	2-Cl-4-MeOPh	
	355[bl]	C-Me	N(CH_2CH_2OMe)$_2$	2-Cl-4-MeOPh	oil
	356[bm]	C-Me	NHCH(Et)CH_2OMe	2-Cl-4-MeOPh	108-110
15	357[bn]	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4-MeOPh	127-129
	358[bo]	C-Me	NEt_2	2-Cl-4-MeOPh	oil
	359[bp]	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	77-79
	360	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4-MeOPh	
	361	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4-MeOPh	
20	362	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh	
	363	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh	
	364	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh	
	365	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh	
	366	C-Me	NHCH(CH_2OMe)$_2$	2-Cl-4,5-(MeO)$_2$Ph	
25	367	C-Me	N(CH_2CH_2OMe)$_2$	2-Cl-4,5-(MeO)$_2$Ph	
	368	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,5-(MeO)$_2$Ph	
	369	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-(MeO)$_2$Ph	
	370	C-Me	NEt_2	2-Cl-4,5-(MeO)$_2$Ph	
	371	C-Me	NH-3-pentyl	2-Cl-4,5-(MeO)$_2$Ph	
30	372	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-(MeO)$_2$Ph	
	373	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-(MeO)$_2$Ph	
	374[bq]	C-Me	NHCH(CH_2OMe)$_2$	2-Br-4,5-(MeO)$_2$Ph	137-138
	375	C-Me	N(CH_2CH_2OMe)$_2$	2-Br-4,5-(MeO)$_2$Ph	
	376[br]	C-Me	NHCH(Et)CH_2OMe	2-Br-4,5-(MeO)$_2$Ph	147-148
35	377	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-(MeO)$_2$Ph	
	378[bs]	C-Me	NEt_2	2-Br-4,5-(MeO)$_2$Ph	52-58

379	C-Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
380	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
381	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
382	C-Me	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
383	C-Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
384	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
385	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph
386	C-Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
387	C-Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
388	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
389	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph
390	C-Me	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
391	C-Me	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
392	C-Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
393	C-Me	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph
395	C-Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph
396	C-Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
397	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
398	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
399	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph
400	C-Me	NEt_2	2-Br-4,6-$(MeO)_2$Ph
401	C-Me	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph
402	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
403	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph
404	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
405	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
406	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
407	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh
408	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh
409	C-Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh
410	C-Me	NEt_2	2-MeO-4-MePh
411	C-Me	NH-3-pentyl	2-MeO-4-MePh
412	C-Me	NHCH(Et)CH_2CH_2OMe	2-MeO-4-MePh
413	C-Me	NHCH(Me)CH_2CH_2OMe	2-MeO-4-MePh
414	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh
415	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh

416	C-Me	NHCH(Et)CH_2OMe	2-Me0-4-MePh	
417	C-Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-MePh	
418	C-Me	NEt_2	2-Me0-4-MePh	
419	C-Me	NH-3-pentyl	2-Me0-4-MePh	
420	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-MePh	
421	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me0-4-MePh	
423[bt]	C-Me	NHCH($CH_2OMe)_2$	2-Me0-4-ClPh	oil
424	C-Me	N($CH_2CH_2OMe)_2$	2-Me0-4-ClPh	
425	C-Me	NHCH(Et)CH_2OMe	2-Me0-4-ClPh	
426	C-Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-ClPh	
427	C-Me	NEt_2	2-Me0-4-ClPh	
428	C-Me	NH-3-pentyl	2-Me0-4-ClPh	
429	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-ClPh	
430	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me0-4-ClPh	

NOTES FOR TABLE 1:

a) Analysis Calcd: C, 52.69, H, 5.17, N, 17.07, Cl, 17.28; Found: C, 52.82, H, 5.06, N, 16.77, Cl, 17.50.

b) CI-HRMS: Calcd: 406.1565, Found: 405.1573 (M + H); Analysis Calcd: C: 59.11; H: 6.20; N: 17.23; Cl: 17.45; Found: C: 59.93; H: 6.34; N: 16.50; Cl: 16.95;
NMR ($CDCl_3$, 300 MHz): 0.95 (t, J = 8, 4H), 1.30-1.40 (m, 4H), 1.50-1.75 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.30-4.45 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H)

c) CI-HRMS: Calcd: 392.1409, Found: 392.1388 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J =8, 3H), 1.35 (t, J = 8, 3H), 1.41 (q, J = 8, 2H), 1.65-1.85 (m, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.20 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).

d) CI-HRMS: Calcd: 404.1409, Found: 404.1408 (M + H);
NMR($CDCl_3$, 300 MHz): 0.35-0.45 (m, 2H), 0.52-0.62 (m, 2H), 0.98 (t, J = 8, 3H), 1.70-1.90 (m, 2H),

2.30 (s, 3H), 2.40 (s, 3H), 3.85-4.02 (m, 2H), 4.02-4.20 (m, 2H), 7.30 (s, 2H), 7.50 (s, 1H).

e) CI-HRMS: Calcd: 424.1307, Found: 424.1307 (M + H): NMR ($CDCl_3$, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.75 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.30 (s, 2H), 7.50 (s, 1H).

f) CI-HRMS: Calcd: 406.1565, Found: 406.1578 (M + H); NMR ($CDCl_3$, 300 MHz): 0.90 (t, J = 8, 3H), 1.00 (t, J = 8, 3H), 1.28-1.45 (m, 4H), 1.50-1.80 (m, 4H), 2.35 (s, 3H), 2.50 (s, 3H), 4.20-4.35 (m, 1H), 6.10-6.23 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

g) CI-HRMS: Calcd: 394.1201, Found: 394.1209 (M + H); NMR ($CDCl_3$, 300 MHz): 1.02 (t, J = 8, 3H), 1.65-1.90 (m, 2H), 2.35 (s, 3H), 2.48 (s, 3H), 3.40 (s, 3H), 3.50-3.60 (m, 2H), 4.35-4.45 (brs, 1H), 6.50-6.60 (m, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

h) CI-HRMS: Calcd: 364.1096, Found: 364.1093 (M + H); Analysis: Calcd: C: 56.05; H: 5.27; N: 19.23; Cl: 19.46; Found: C: 55.96; H: 5.24; N: 18.93; Cl: 19.25;
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.30 (3, 3H), 2.40 (s, 3H), 3.95-4.15 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

i) CI-HRMS: Calcd: 438.1464, Found: 438.1454 (M + H); NMR ($CDCl_3$, 300 MHz): 1.22 (t, J = 8, 6H), 2.35 (s, 3H), 2.47 (s, 3H), 3.39 (q, J = 8, 4H), 3.65 (dd, J = 8, 1, 2H), 3.73 (dd, J = 8, 1, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8, 1H), 7.30 (d, J = 1, 2H), 7.50 (s, 1H).

j) CI-HRMS: Calcd: 378.1252, Found: 378.1249 (M + H); Analysis: Calcd: C: 57.15; H: 5.61; N: 18.51; Cl: 18.74; Found: C: 57.56; H: 5.65; N: 18.35; Cl: 18.45;
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.35 (s, 3H), 2.50

(s, 3H), 4.15-4.25 (m, 1H), 6.18 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (s, 1H).

k) CI-HRMS: Calcd: 398.0939, Found: 398.0922 (M + H); Analysis: Calcd: C: 60.31; H: 4.30; N: 17.58; Cl: 17.80; Found: C: 60.29; H: 4.59; N: 17.09; Cl: 17.57;
NMR ($CDCl_3$, 300 MHz): 2.05 (s, 3H), 2.50 (s, 3H), 3.78 (s, 3H), 7.20-7.45 (m, 7H), 7.50 (d, J = 1, 1H).

l) CI-HRMS: Calcd: 392.1409, Found: 392.1391 (M + H); NMR ($CDCl_3$, 300 MHz): 0.98 (t, J = 8, 6H), 1.70-1.85 (m, 4H), 2.30 (s, 3H), 2.40 (s, 3H), 3.80-4.10 (m, 4H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

m) CI-HRMS: Calcd: 392.1409, Found: 392.1415 (M + H); Analysis: Calcd: C: 58.17; H: 5.92; N: 17.85; Cl: 18.07; Found: C: 58.41; H: 5.85: N: 18.10; Cl: 17.75;
NMR ($CDCl_3$, 300 MHz): 0.90-1.05 (m, 6H), 1.35-1.55 (m, 2H), 1.55-1.85 (m, 4H), 2.35 (s, 3H), 2.48 (s, 3H), 4.20-4.35 (m, 1H), 6.15 (d, J = 8, 1H), 7.30 (s, 2H), 7.50 (d, J = 1, 1H).

n) CI-HRMS: Calcd: 337.0623, Found: 337.0689 (M + H); Analysis: Calcd: C: 53.43; H: 4.18; N: 16.62; Cl: 21.03, Found: C: 53.56; H: 4.33; N: 16.56; Cl: 20.75;
NMR ($CDCl_3$, 300 MHz): 1.60 (t, J = 8, 3H), 2.40 (s, 3H), 2.55 (s, 3H), 4.80 (q, J = 8, 2H), 7.30 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.55 (d, J = 1, 1H).

o) CI-HRMS: Calcd: 383.2321, Found: 383.2309 (M + H); NMR ($CDCl_3$, 300 MHz): 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.61 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.94 (s, 2H).

p) CI-HRMS: Calcd: 370.2243, Found: 370.2246 (M + H);

Analysis: Calcd: C: 65.02; H: 7.38; N: 18.96;
Found: C: 65.22; H: 7.39; N: 18.71;
NMR ($CDCl_3$, 300 MHz): 2.18 (s, 3H), 2.30 (s, 3H), 2.45 (s, 3H), 3.45 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.69 (dd, J = 8, 8, 2H), 4.60-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.10 (s, 1H).

q) CI-HRMS: Calcd: 384.2400, Found: 384.2393 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.16 (s, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 3.40 (s, 6H), 3.77 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.02 (d, J = 8, 1H) 7.05 (s, 1H), 7.10 (d, J = 7, 1H).

r) CI-HRMS: Calcd: 354.2294, Found: 354.2271 (M + H);
Analysis: Calcd: C: 67.96; H: 7.71; N: 19.81;
Found: C: 67.56; H: 7.37; N: 19.60;
NMR ($CDCl_3$, 300 MHz): 1.03 (t, J = 8, 3H), 1.65-1.88 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 3.40 (s, 3H), 3.50-3.62 (m, 2H), 4.30-4.45 (m, 1H), 6.51 (d, J = 8, 1H), 7.04 (d, J = 8, 1H), 7.10 (d, J =8, 1H), 7.12 (s, 1H).

s) CI-HRMS: Calcd: 338.2345, Found: 338.2332 (M + H);
Analysis: Calcd: C: 71.18; H: 8.06; N: 20.75;
Found: C: 71.43; H: 7.80; N: 20.70;
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.19 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.15-4.26 (m, 1H), 6.17 (d, J = 8, 1H), 7.06 (d, J = 8, 1H), 7.10 (d, J = 1, 1H), 7.13 (s, 1H).

t) CI-HRMS: Calcd: 324.2188, Found: 324.2188 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.25 (t, J = 8, 6H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.95-4.20 (m, 4H), 7.05 (dd, J = 8, 1, 1H), 7.07 (s, 1H), 7.10 (d, J = 1, 1H)

u) CI-HRMS: Calcd: 346.1780, Found: 346.1785 (M + H);
Analysis: Calcd: C: 66.07; H: 5.54; N: 28.39;
Found: C: 66.07; H: 5.60; N: 27.81;

NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.32 (s, 3H) 2.17 (s, 3H), 2.52 (s, 3H), 5.25-5.35 (m, 4H), 7.08 (s, 2H), 7.15 (s, 1H).

v) CI-HRMS: Calcd: 340.2137, Found: 340.2137 (M + H); Analysis: Calcd: C: 67.23; H: 7.42; N: 20.63; Found:C: 67.11; H: 7.39; N: 20.26; NMR ($CDCl_3$, 300 MHz): 1.40 (d, J = 8, 3H), 2.16 (s, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 3.42 (s, 3H), 3.50-3.60 (m, 2H), 4.50-4.15 (m, 1H), 6.56 (d, J = 8, 1H), 7.00-7.15 (m, 3H).

w) CI-HRMS: Calcd: 355.2134, Found: 355.2134 (M + H); NMR ($CDCl_3$, 300 MHz): 1.05 (t, J = 8, 3H), 1.85-2.00 (m, 2H), 2.17 (s, 3H), 2.36 (s, 6H), 2.50 (s, 3H), 3.41 (s, 3H), 3.45 (dd, J = 8, 3, 1H), 3.82 (dd, J = 8, 1, 1H), 5.70-5.80 (m, 1H), 7.00-7.20 (m, 3H).

x) CI-HRMS: Calcd: 364.2501, Found: 364.2501 (M + H); NMR ($CDCl_3$, 300 MHz): 0.35-0.43 (m, 2H), 0.50-0.60 (m, 2H), 0.98 (t, J = 8, 3H), 1.20-1.30 (m, 1H), 1.72-1.90 (m, 2H), 2.18 (s, 3H) 2.28 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 3.88-4.03 (m, 2H), 4.03-4.20 (m, 2H), 7.00-7.15 (m, 3H).

y) CI-HRMS: Calcd: 353.2454, Found: 353.2454 (M + H); Analysis: Calcd: C: 68.15; H: 8.02; N: 23.84; Found: C: 67.43; H: 7.81; N: 23.45; NMR ($CDCl_3$, 300 MHz): 1.38 (d, J = 8, 3H), 2.18 (s, 3H), 2.30-2.40 (m, 12H), 2.47 93, 3H), 2.60-2.75 (m, 2H), 4.30-4.50 (m, 1H), 6.60-6.70 (m, 1H), 7.00-7.15 (m, 3H).

z) CI-HRMS: Calcd: 361.2140, Found: 361.2128 (M + H); NMR ($CDCl_3$, 300 MHz): 0.75-0.83 (m, 2H), 1.00-1.10 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 2.85 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.40-4.55 (m, 2H), 7.00-7.18 (m, 3H).

aa) CI-HRMS: Calcd: 363.2297, Found: 363.2311 (M + H);

NMR ($CDCl_3$, 300 MHz): 1.01 (t, 3H, J=8), 1.75-1.90 (m,2H), 2.15 (s,3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.98 (t, 2H, J = 8), 3.97-4.15 (m, 2H), 4.15-4.30 (m, 2H), 7.03(d, 1H, 1H), 7.08 (d, 1H, J = 8), 7.10 (s, 1H).

ab) CI-HRMS: Calcd: 363.2297, Found: 363.2295 (M + H); NMR ($CDCl_3$, 300 MHz): 1.01 (t, 3H, J = 8), 1.35-1.55 (m, 2H), 1.75-1.90 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 2.46 (s, 3H), 4.10-4.30 (m, 2H), 4.95-5.10 (br s, 2H), 7.05 (d, 1H, J = 8), 7.10 (d, 1H, J = 8), 7.15 (s, 1H).

ac) CI-HRMS: Calcd: 368.2450, Found: 368.2436; Analysis: Calcd: C, 68.62, H, 7.95, N, 19.06; Found: C, 68.73, H, 7.97, N, 19.09; NMR ($CDCl_3$, 300 MHz): 1.05 (t, J = 8, 3H), 1.70-1.90 (m, 2H), 2.01 (d, J = 3, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46, 2.465 (s, s, 3H), 3.42, 3.48 (s, s, 3H), 3.53-3.63 (m, 2H), 4.35-4.45 (m, 1H), 6.73 (d, J = 8, 1H), 6.97 (s, 2H).

(ad) CI- HRMS: Calcd: 352.2501, Found: 352.2500 (M + H): Analysis: Calcd: C: 71.76; H: 8.33; N: 19.92, Found: C: 71.55; H: 8.15; N: 19.28; NMR ($CDCl_3$, 300 MHz): 1.01(t, J = 8, 6H), 1.58 -1.70 (m, 2H), 1.70-1.85 (m, 2H), 2.02 (s, 6H), 2.19 (s, 3H), 2.45 (s, 3H), 4.12-4.28 (m, 1H), 6.18 (d, J = 8, 1H), 6.95 (s, 2H).

(ae) CI- HRMS: Calcd: 398.2556, Found: 398.2551 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62, Found: C: 66.74; H: 7.79; N: 17.70; NMR ($CDCl_3$, 300 MHz): 2.00 (s, 6H), 2.12 (s, 3H), 2.30 (s, 3H), 2.37 (s, 3H), 3.40 (s, 6H), 3.78 (t, J = 8, 4H), 4.25-4.40 (m, 4H), 6.93 (s, 2H).

(af) CI-HRMS: Calcd: 450.1141, Found: 450.1133 (M + H); Analysis: Calcd: C: 50.67; H: 5.37; N: 15.55; Br: 17.74; Found: C: 52.36; H: 5.84; N: 14.90; Br: 17.44;

NMR ($CDCl_3$, 300 MHz): 2.32 (s, 3H), 2.57 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.69 (q, J = 8, 2H), 3.82 (s, 3H), 4.60-4.70 (m, 1H), 6.73 (d, J = 8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.22 (d, J = 8, 1H).

ag) CI-HRMS: Calcd: 434.1192, Found: 434.1169 (M + H); Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.57; H: 5.60; N: 15.98; Br: 18.22;
NMR ($CDCl_3$, 300 MHz): 1.00-1.07 (m, 3H), 1.65-1.85 (m, 2H), 2.35 (s, 3H), 2.46, 2.47 (s, s, 3H), 3.40, 3.45 (s, s, 3H), 3.83 (s, 3H), 4.35-4.45 (m, 1H), 6.55 (d, J = 8, 1H), 6.92 (dd, J = 8, 1, 1H), 7.20-7.30 (m, 2H).

ah) CI-HRMS: Calcd: 337.2266, Found: 337.2251 (M + H); Analysis: Calcd: C: 70.18; H: 8.06; N: 20.75; Found: C: 70.69; H: 7.66; N: 20.34;
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.01 (s, 6H), 2.15 (s, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.07 (q, J = 8, 4H), 6.93 (s, 2H).

ai) CI-HRMS: Calcd: 412.2713, Found: 412.2687 (M + H); Analysis: Calcd: C: 67.13; H: 8.08; N: 17.02; Found : C: 67.22; H: 7.85; N: 17.13;
NMR ($CDCl_3$, 300 MHz):1.24 (t, J = 8, 6H), 2.00 (s, 6H), 2.20 (s, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 3.60 (q, J = 8, 4H), 3.66 (dd, J = 8, 3, 2H), 3.75 (dd, J = 8, 3, 2H), 4.55-4.65 (m, 1H), 6.75 (d, J = 8, 1H), 6.95 (s, 2H).

aj) CI-HRMS: Calcd: 398.2556, Found: 398.2545 (M + H); Analysis: Calcd: C: 66.47; H: 7.86; N: 17.62; Found: C: 66.87; H: 7.62; N: 17.75;
NMR ($CDCl_3$, 300 MHz): 1.95-2.10 (m, 8H), 2.20 (s, 3H), 2.32 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.42 (s, 3H), 3.50-3.70 (m, 4H), 4.58-4.70 (m, 1H), 6.87 (d, J = 8, 1H), 6.95 (s, 2H).

ak) CI-HRMS: Calcd: 338.1981, Found: 338.1971 (M + H);

Analysis: Calcd: C: 67.63; H: 6.87; N: 20.06;
Found: C: 67.67; H: 6.82; N: 20.31;
NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.29 (s, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 3.90 (t, J = 8, 4H), 4.35-4.45 (m, 4H), 7.00-7.15 (m, 3H).

al) CI-HRMS: Calcd: 464.1297, Found: 464.1297 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.28 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.75 (t, J = 8, 4H), 3.83 (s, 3H), 4.20-4.50 (m, 4H), 6.93 (dd, J = 8, 1, 1H), 7.20 (s, 1H), 7.24 (d, J = 1, 1H).

am) CI-HRMS: Calcd: 418.1242, Found: 418.1223 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.00 (t, d, J = 8, 1, 6H), 1.55-1.75 (m, 4H), 2.34 (s, 3H), 2.49 (s, 3H), 2.84 (s, 3H), 4.15-4.27 (m, 1H), 6.19 (d, J = 8, 1H), 6.93 (dd, J = 8, 1, 1H), 7.21-7.30 (m, 2H).

an) CI-HRMS: Calcd: 404.1086, Found: 404.1079(M + H);
NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.28 (s, 3H), 2.40 (s, 3H), 3.83 (s, 3H), 3.90-4.08 (m, 2H), 4.08-4.20 (m, 2H), 6.92 (dd, J = 8, 1, 1H), 7.20-7.25 (m, 2H).

ao) CI-HRMS: Calcd: 308.1875, Found: 308.1872 (M + H);
NMR ($CDCl_3$, 300 MHz): 0.75-0.80 (m, 2H), 0.93-1.00 (m, 2H), 2.16 (s, 3H), 2.28 (s, 3H), 2.35 (s, 3H), 2.53 (s, 3H), 3.00-3.10 (m, 1H), 6.50-6.55 (m, 1H), 7.00-7.15 (m, 3H).

ap) CI-HRMS: Calcd: 397.1988, Found: 397.1984 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.43 (s, 3H), 2.50 (s, 3H), 3.43 (s, 3H), 3.61 (dd, J = 8, 8, 2H), 3.69 (dd,J = 8, 8, 2H), 3.88 (s, 3H), 4.58-4.70 (m, 1H), 6.75 (d, J = 8, 1H), 7.20 (dd, J = 8, 1, 1H), 7.25 (d, J = 1, 1H), 7.40 (s, 1H).

aq) CI-HRMS: Calcd: 375.2297, Found: 375.2286 (M + H);
Analysis: Calcd: C: 70.56; H: 7.01; N: 22.44;
Found: C: 70.49; H: 6.99; N: 22.45;
NMR ($CDCl_3$, 300 MHz): 0.79-0.85 (m, 2H), 1.00-1.05 (m, 1H), 2.00 (s, 6H), 2.19 (s, 3H), 2.32 (s, 3H),

2.44 (s, 3H), 2.84 (t, J = 8, 2H), 3.30-3.40 (m, 1H), 4.50 (t, J = 8, 2H), 6.95 (s, 2H).

ar) CI-HRMS: Calcd: 434.1192, Found: 434.1189 (M + H); Analysis: Calcd: C: 52.54; H: 5.58; N: 16.12; Br: 18.40; Found: C: 52.75; H: 5.59; N: 16.09; Br: 18.67;
NMR ($CDCl_3$, 300 MHz): 2.19 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.43 (s, 6H), 3.60 (dd, J = 8, 8, 2H), 3.70 (dd, J = 8,8, 2H), 4.58-4.70 (m, 1H), 6.71 (d, J = 8, 1H), 7.08 (d, J = 8, 1H), 7.37 (dd, J = 8, 1, 1H), 7.45 (d, J = 1, 1H).

as) CI-HRMS: Calcd: 448.1348, Found: 448.1332 (M + H); Analysis: Calcd: C: 53.58; H: 5.85; N: 16.62; Br: 17.82; Found: C: 53.68; H: 5.74; N: 15.52; Br: 13.03;
NMR ($CDCl_3$, 300 MHz): 1.95-2.10 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.47 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.67 (m, 4H), 4.55-4.70 (m, 1H), 6.89 (d, J = 8, 1H), 7.05 (d, J = 8, 1H), 7.35 (dd, J = 8, 1, 1H), 7.47 (d, J = 1, 1H).

at) CI-HRMS: Calcd: 400.2349, Found: 400.2348 (M + H); Analysis: Calcd: C: C: 63.14; H: 7.32; N: 17.53; Found: C:63.40; H: 7.08; N: 17.14;
NMR ($CDCl_3$, 300 MHz): 2.16 (s, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 3.42 (s, 6H), 3.60 (q, J = 8, 2H), 3.70 (q, J = 8, 2H), 3.85 (s, 3H), 4.59-4.70 (m, 1H), 6.70 (d, J = 8, 1H), 6.76 (s, 1H), 6.96 (s, 1H).

au) CI-HRMS: Calcd: 414.2505, Found: 414.2493 (M + H);
NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 2.19 (s, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 3.84 (s, 3H), 4.20-4.45 (m, 4H), 6.77 (s, 1H), 6.93 (s, 1H).

av) CI-HRMS: Calcd: 368.2450, Found: 368.2447 (M + H);
NMR ($CDCl_3$, 300 MHz): 1.00 (t, J = 8, 6H), 1.55-1.85 (m, 4H), 2.19 (s, 3H), 2.20 (s, 3H), 2.30 (s,

3H), 2.47 (s, 3H), 3.88 (s, 3H), 4.10-4.30 (m, 1H), 6.15 (d, J = 8, 1H), 6.78 (s, 1H), 6.98 (s, 1H).

aw) CI-HRMS: Calcd: 353.2216, Found: 353.2197 (M + H); NMR ($CDCl_3$, 300 MHz): 1.35 (t, J = 8, 6H), 2.17 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90-4.20 (m, 4H), 6.78 (s, 1H), 6.95 (s, 1H).

ax) CI-HRMS: Calcd: 390.1697, Found: 390.1688 (M + H); Analysis: Calcd: C: 58.53; H: 6.20; N: 17.96; Cl: 9.09; Found: C: 58.95; H: 6.28; N: 17.73; Cl: 9.15; NMR ($CDCl_3$, 300 MHz): 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.42 (s, 6H), 3.60 (dd, J = 8, 8, 2H) 3.68 (dd, J = 8, 8, 2H), 4.59-4.72 (m, 1H), 6.72 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.23 (d, J = 8, 1H), 7.32 (s, 1H).

ay) CI-HRMS: Calcd: 374.1748, Found: 374.1735 (M + H); Analysis: Calcd: C: 61.04; H: 6.47; N: 18.73; Cl: 9.48; Found: C: 61.47; H: 6.54; N: 18.23; Cl: 9.61; NMR ($CDCl_3$,300 MHz): 1.01 (t, J = 8, 3H), 1.62-1.88 (m, 4H), 2.35 (s, 3H), 2.37 (s, 3H), 2.48 (d, J = 1, 3H), 3.40, 3.45 (s, s, 3H), 3.50-3.64 (m, 2H), 4.38-4.47 (m, 1H), 6.53 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.07 (d, J = 8, 1H), 7.12 (s, 1H).

az) CI-HRMS: Calcd: 404.1853, Found: 404.1839 (M + H); NMR ($CDCl_3$, 300 MHz): 2.29 (s, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 3.40 (s, 6H), 3.76 (t, J = 8, 4H), 4.20-4.45 (m, 4H), 7.11 (d, J = 8, 1H), 7.22 (d, J = 8, 1H), 7.31 (s, 1H).

ba) CI-HRMS: Calcd: 404.1853, Found: 404.1859 (M + H); Analysis: C: 59.47; H: 6.50; N: 17.34; Cl: 8.79; Found: C: 59.73; H: 6.46; N: 17.10; Cl: 8.73; NMR ($CDCl_3$, 300 MHz): 1.95-2.08 (m, 2H), 2.35 (s, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.50-3.65 (m, 4H), 4.56-4.70 (m, 1H), 6.85 (d, J = 8, 1H), 7.12 (d, J = 8, 1H), 7.45 (d, J = 8, 1H), 7.32 (s, 1H).

bb) CI-HRMS: Calcd: 391.2246, Found: 391.2258 (M + H); Analysis: C: 67.67; H: 6.71; N: 21.52; Found: C: 67.93; H: 6.70; N: 21.48;
NMR ($CDCl_3$, 300 MHz): 0.76-0.84 (m, 2H), 0.84-0.91 (m, 2H), 1.00-1.08 (m, 2H), 2.15 (s, 3H), 2.20 (s, 3H), 2.29 (s, 3H), 2.45 (s, 3H), 2.85 (t, J = 8, 2H), 3.28-3.30 (m, 1H), 3.85 (s, 3H), 6.78 (s, 1H), 6.95 (s, 1H).

bc) CI-HRMS: Calcd: 386.2192, Found: 386.2181 (M + H); Analysis: C: 62.32; H: 7.06; N: 18.17; Found: C: 62.48; H: 6.83; N: 18.15;
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.7 (br.d, 1H, J = 8), 4.7-4.6 (m, 1H), 3.85 (s, 3H), 3.70-3.55 (m, 4H), 3.45 (s, 6H), 2.5 (s, 3H), 2.3 (s, 3H), 2.15 (s, 3H).

bd) CI-HRMS: Calcd: 400.2349, Found: 400.2336 (M + H);
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 7), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 7,1), 4.45-4.25 (br.s, 4H), 3.75 (t, 4H, J = 7), 3.4 (s, 6H), 2.4 (s, 3H), 2.25 (s, 3H), 2.15 (s, 3H).

be) CI-HRMS: Calcd: 370.2243, Found: 370.2247 (M + H); Analysis: C: 65.02; H: 7.38; N: 18.96; Found: C: 65.28; H: 7.27; N: 18.71;
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 6.5 (br. d, 1H, J = 1), 4.5-4.3 (m, 1H), 3.85 (s, 3H), 3.65-3.5 (m, 2H), 3.4 (s, 2H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.9-1.7 (m, 2H), 1.05 (t, 3H, J = 7).

bf) CI-HRMS: Calcd: 379.2246, Found: 379.2248 (M + H);
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.3-4.0 (m, 4H), 3.85 (s, 3H), 3.0 (t, 2H, J = 7), 2.45 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.9-1.8 (m, 2H), 1.0 (t, 3H, J = 7).

bg) CI-HRMS: Calcd: 340.2137, Found: 340.2122 (M + H);

NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8,1), 4.2-4.0 (br.m, 4H), 3.85 (s, 3H, 2.4 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.35 (t, 6H, J = 7).

bh) CI-HRMS: Calcd: 313.1665, Found: 313.6664 (M + H).

bi) CI-HRMS: Calcd: 400.2349, Found: 400.2346 (M + H); NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 7), 6.9-6.75 (m, 3H), 4.7-4.55 (m, 1H), 3.8 (s, 3H), 3,7-3.5 (m, 4H), 3.45 (s, 3H), 3.35 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 2.1-1.95 (m, 2H).

bj) CI-HRMS: Calcd: 377.2090, Found: 377.2092 (M + H); Analysis: C: 67.00; H: 6.44; N: 22.32; Found: C: 67.35; H: 6.44; N: 22.23;
NMR ($CDCl_3$, 300 MHz): 7.1 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.8 (dd, 1H, J = 8,1), 4.55-4.4 (m, 2H), 3.85 (s, 3H), 3.4-3.3 (m, 1H), 2.85 (t, 2H, J = 7), 2.5 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H), 1.1-1.0 (m, 2H), 0.85-0.75 (m, 2H).

bk) CI-HRMS: Calcd: 413.2427, Found: 413.2416 (M + H); NMR ($CDCl_3$, 300Hz): 7.1 (d, 1H, J = 8), 6.85 (d, 1H, J = 1), 6.75 (dd, 1H, J = 8,1), 4.6 (m, 1H), 3.85 (s, 3H), 3.75-3.6(m, 4H), 3.6 (q, 4H, J = 7), 2.5 (s, 3H), 2.3 s, 3H), 2.2 (s, 3H), 1.25 (t, 6H, J = 7).

bl) CI-HRMS: Calcd: 420.1802, Found: 420.1825(M + H);

bm) CI-HRMS: Calcd: 390.1697, Found: 390.1707(M + H);

bn) CI-HRMS: Calcd: 397.1465, Found: 397.1462(M + H);

bo) CI-HRMS: Calcd: 360.1513, Found: 360.1514(M + H);

bp) CI-HRMS: Calcd: 374.1748, Found: 374.1737(M + H);

bq) CI-HRMS: Calcd: 479.1155, Found: 479.1154(M + H);

br) CI-HRMS: Calcd: 463.1219, Found: 463.1211(M + H); Analysis Calcd: C: 51.96, H: 5.23, N, 15.15, Br: 17.28; Found: C: 52.29, H: 5.62, N: 14.79, Br: 17.47

bs) CI-HRMS: Calcd: 433.1113, Found: 433.1114(M, ^{79}Br);

bt) NH_3-CI MS: Calcd: 406, Found: 406 (M + H)+;

NMR ($CDCl_3$, 300 MHz) : δ 7.28 (d, J=10Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.7 (d, J=9, 1H), 4.63 (m, 1H), 3.79 (s, 3H), 3.6 (m, 4H), 3.42 (s, 6H), 2.47 (s, 3H), 2.32 (s, 3H).

EXAMPLE 431

Preparation of 2,4,7-dimethyl-8-(4-methoxy-2-methylphenyl)[1,5-a]-pyrazolo-1,3,5-triazine (Formula 1, where R^3 is CH_3, R_1 is CH_3, Z is C-CH_3, Ar is 2,4-dimethylphenyl)

5-Acetamidino-4-(4-methoxy-2-methylphenyl)-3-methylpyrazole, acetic acid salt (602 mg, 2 mmol) was mixed with a saturated $NaHCO_3$ solution (10 mL). The aqueous mixture was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was taken up in toluene (10 mL) and trimethyl orthoacetate (0.36 g, 3 mmol) was added to the suspension. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and stirred for 16 hours. After being cooled to ambient temperature, the reaction mixture was concentrated in vacuo to give an oily solid. Column chromatography ($CHCl_3$:MeOH::9:1) afforded, after removal of solvent in vacuo, a yellow viscous oil (Rf = 0.6, 210 mg, 37% yield): NMR ($CDCl_3$, 300 MHz): 7.15 (d, 1H, J = 8), 6.9 (d, 1H, J = 1), 6.85 (dd, 1H, J = 8,1), 3.85 (s, 3H), 2.95 (s, 3H), 2.65 (s, 3H), 2.4 (s, 3H), 2.15 (s, 3H); CI-HRMS: Calcd: 283.1559, Found: 283.1554 (M + H).

EXAMPLE 432

7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (Formula 1 where A is CH, R1 is Me, R3 is OH, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

5-Amino-4-(2-chloro-4-methylphenyl)-3-methylpyrazole (1.86 g, 8.4 mmol) was dissolved in glacial acetic acid (30 mL) with stirring. Ethyl acetoacetate (1.18 mL, 9.2 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (1.0 g, 42% yield): NMR ($CDCl_3$, 300Hz): 8.70 (br.s 1H), 7.29 (s, 1H), 7.21-7.09 (m, 2H), 5.62 (s, 1H), 2.35 (s, 6H), 2.29 (s, 3H); CI-MS: 288 (M+H).

EXAMPLE 433

7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (Formula 1 where A is CH, R1 is Me, R3 is Cl, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A mixture of 7-hydroxy-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (1.0 g, 3.5 mmol), phosphorus oxychloride (2.7 g, 1.64 mL, 17.4 mmol), N,N-diethylaniline (0.63 g, 0.7 mL, 4.2 mmol) and toluene (20 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:2) on the residue gave 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (900 mg, 84% yield) as a yellow oil: NMR

($CDCl_3$, 300Hz): 7.35 (s, 1H), 7.28-7.26 (m, 1H), 71.6 (d, 1H, J = 7), 6.80 (s, 1H), 2.55 (s, 3H), 2.45 (s, 3H), 2.40 (s, 3H); CI- MS: 306 (M+H).

EXAMPLE 434

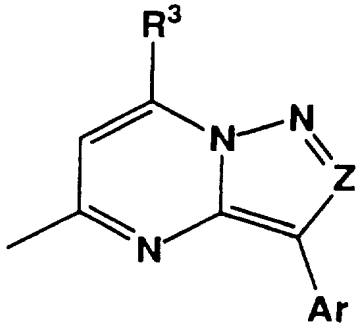
7-(pentyl-3-amino)-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine

(Formula 1 where A is CH, R1 is Me, R3 is pentyl-3-amino, Z is C-Me, Ar is 2-chloro-4-methylphenyl)

A solution of 3-pentylamine (394mg, 6.5 mmol) and 7-chloro-5-methyl-3-(2-chloro-4-methylphenyl)pyrazolo[1,5-a]pyrimidine (200 mg, 0.65 mmol) in dimethylsulfoxide (DMSO, 10 mL) was stirred at 150°C for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over $MgSO_4$, filtration and removal of solvent in vacuo produced a yellow solid. Flash chromatography (EtOAc:hexanes::1:4) afforded a white solid (140 mg, 60% yield): mp 139-141°C; NMR ($CDCl_3$, 300Hz):7.32 (s, 1H), 7.27 (d, 1H, J = 8), 7.12 (d, 1H, J = 7), 6.02 (d, 1H, J = 9), 5.78 (s, 1H), 3.50-3.39 (m, 1H), 2.45 (s, 3H), 2.36 (s, 6H), 1.82-1.60 (m, 4H), 1.01 (t, 6H, J = 8); Analysis Calcd for $C_{20}H_{25}ClN_4$: C, 67.31, H, 7.06, N, 15.70, Cl: 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

The examples delineated in TABLE 2 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 2



Ex.	Z	R3	Ar	mp (°C)
435[b]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph	71-73
436[c]	C-Me	N(Bu)Et	2,4-Cl_2-Ph	86-87
437[d]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph	110-111
438[e]	C-Me	$N(Pr)CH_2CH_2CN$	2,4-Cl_2-Ph	83-85
439[f]	C-Me	NH-3-pentyl	2,4-Cl_2-Ph	175-176
440[g]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	107
441[h]	C-Me	$NHCH(Et)_2$	2,4-Me_2-Ph	oil
442[i]	C-Me	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph	103-105
443[j]	C-Me	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph	87-89
444[k]	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2,4-Me_2-Ph	133 (dec)
445[l]	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl,4-MePh	77-78
446[m]	C-Me	$NHCH(CH_2OMe)_2$	2-Cl,4-MePh	131-133
447[n]	C-Me	$NHCH(Et)_2$	2-Cl,4-MePh	139-141
448[o]	C-Me	NEt_2	2,4-Me_2-Ph	92-94
449[p]	C-Me	$N(Pr)CH_2CH_2CN$	2,4-Me_2-Ph	143-144
450[q]	C-Me	$N(Bu)CH_2CH_2CN$	2,4-Me_2-Ph	115-117
451[r]	C-Me	$NHCH(Et)CH_2OMe$	2,4-Me_2-Ph	oil
452[s]	C-Me	$NHCH(Et)_2$	2-Me,4-MeOPh	104-106
453[t]	C-Me	$NHCH(CH_2OMe)_2$	2-Me,4-MeOPh	115-116
454[u]	C-Me	$N(CH_2CH_2OMe)_2$	2-Me,4-MeOPh	oil
455[v]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2-Me,4-MeOPh	oil
456[w]	C-Me	(S)-$NHCH(CH_2CH_2OMe)$-(CH_2OMe)	2,4-Me_2-Ph	oil

	457[x]	C-Me	N(CH$_2$CH$_2$OMe)$_2$	2-Me,4-ClPh	oil
	458[y]	C-Me	NHEt	2,4-Me$_2$-Ph	oil
	459[z]	C-Me	NHCH(Et)$_2$	2-Me,4-ClPh	94-96
	460[aa]	C-Me	NHCH(CH$_2$OMe)$_2$	2-Me,4-ClPh	113-114
	461[ab]	C-Me	N(Ac)Et	2,4-Me$_2$-Ph	oil
	462[ac]	C-Me	(S)-NHCH(CH$_2$CH$_2$OMe)-(CH$_2$OMe)	2-Me,4-ClPh	oil
	463[ad]	C-Me	N(Pr)CH$_2$CH$_2$CN	2-Me,4-MeOPh	118-119
	464[ae]	C-Me	NEt$_2$	2-Me,4-MeOPh	97-99
	465[af]	C-Me	(S)-NHCH(CH$_2$CH$_2$OMe)-(CH$_2$OMe)	2-Cl,4-MePh	101-103
	466[ag]	C-Me	NEt$_2$	2-Cl,4-MePh	129-130
	467[ah]	C-Me	N(c-Pr)CH$_2$CH$_2$CN	2-Me,4-MeOPh	177-178
	468[ai]	C-Me	N(c-Pr)CH$_2$CH$_2$CN	2-Cl,4-MePh	162-163
	469[aj]	C-Me	NHCH(Et)CH$_2$OMe	2-Me,4-MeOPh	oil
	470[ak]	C-Me	NHCH(Et)CH$_2$OMe	2-Cl,4-MePh	111-113
	471	C-Me	NHCH(CH$_2$OMe)$_2$	2-Cl-4-MeOPh	
	472	C-Me	N(CH$_2$CH$_2$OMe)$_2$	2-Cl-4-MeOPh	
	473	C-Me	NHCH(Et)CH$_2$OMe	2-Cl-4-MeOPh	
	474	C-Me	N(c-Pr)CH$_2$CH$_2$CN	2-Cl-4-MeOPh	
	475	C-Me	NEt$_2$	2-Cl-4-MeOPh	
	476	C-Me	NH-3-pentyl	2-Cl-4-MeOPh	
	477	C-Me	NHCH(Et)CH$_2$CH$_2$OMe	2-Cl-4-MeOPh	
	478	C-Me	NHCH(Me)CH$_2$CH$_2$OMe	2-Cl-4-MeOPh	
	479	C-Me	NHCH(Et)CH$_2$CH$_2$OMe	2-Br-4-MeOPh	
	480	C-Me	NHCH(Me)CH$_2$CH$_2$OMe	2-Br-4-MeOPh	
	481	C-Me	NHCH(Et)CH$_2$CH$_2$OMe	2-Me-4-MeOPh	
	482	C-Me	NHCH(Me)CH$_2$CH$_2$OMe	2-Me-4-MeOPh	
	483	C-Me	NHCH(CH$_2$OMe)$_2$	2-Cl-4,5-(MeO)$_2$Ph	
	484	C-Me	N(CH$_2$CH$_2$OMe)$_2$	2-Cl-4,5-(MeO)$_2$Ph	
	485	C-Me	NHCH(Et)CH$_2$OMe	2-Cl-4,5-(MeO)$_2$Ph	
	486	C-Me	N(c-Pr)CH$_2$CH$_2$CN	2-Cl-4,5-(MeO)$_2$Ph	
	487	C-Me	NEt$_2$	2-Cl-4,5-(MeO)$_2$Ph	99-101
	488	C-Me	NH-3-pentyl	2-Cl-4,5-(MeO)$_2$Ph	169-170
	489	C-Me	NHCH(Et)CH$_2$CH$_2$OMe	2-Cl-4,5-(MeO)$_2$Ph	

	490	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph	
	491	C-Me	NHCH$(CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph	90-93
	492	C-Me	N$(CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph	110
	493	C-Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
5	494	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph	
	495	C-Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph	
	496	C-Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph	
	497	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
	498	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,5-$(MeO)_2$Ph	
10	499	C-Me	NHCH$(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph	
	500	C-Me	N$(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph	
	501	C-Me	NHCH(Et)CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
	502	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,6-$(MeO)_2$Ph	
	503	C-Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph	
15	504	C-Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph	
	505	C-Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
	506	C-Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,6-$(MeO)_2$Ph	
	507	C-Me	NHCH$(CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph	
	508	C-Me	N$(CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph	
20	509	C-Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
	510	C-Me	N(c-Pr)CH_2CH_2CN	2-Me-4,6-$(MeO)_2$Ph	
	511	C-Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph	
	512	C-Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph	
	513	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
25	514	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4,6-$(MeO)_2$Ph	
	515	C-Me	N(c-Pr)CH_2CH_2CN	2-Br-4,6-$(MeO)_2$Ph	
	516	C-Me	NEt_2	2-Br-4,6-$(MeO)_2$Ph	
	517	C-Me	NH-3-pentyl	2-Br-4,6-$(MeO)_2$Ph	
	518	C-Me	NHCH(Et)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph	
30	519	C-Me	NHCH(Me)CH_2CH_2OMe	2-Br-4,6-$(MeO)_2$Ph	
	520	C-Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh	
	521	C-Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh	
	522	C-Me	NHCH$(CH_2OMe)_2$	2-MeO-4-MePh	
	523	C-Me	N$(CH_2CH_2OMe)_2$	2-MeO-4-MePh	
35	524	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-MePh	
	525	C-Me	N(c-Pr)CH_2CH_2CN	2-MeO-4-MePh	

526	C-Me	NEt_2	2-MeO-4-MePh
527	C-Me	NH-3-pentyl	2-MeO-4-MePh
528	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-MePh
529	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
530	C-Me	$NHCH(CH_2OMe)_2$	2-MeO-4-MePh
531	C-Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-MePh
532	C-Me	$NHCH(Et)CH_2OMe$	2-MeO-4-MePh
533	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-MePh
53f	C-Me	NEt_2	2-MeO-4-MePh
535	C-Me	NH-3-pentyl	2-MeO-4-MePh
536	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-MePh
537	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
538	C-Me	$NHCH(CH_2OMe)_2$	2-MeO-4-ClPh
539	C-Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
540	C-Me	$NHCH(Et)CH_2OMe$	2-MeO-4-ClPh
541	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-ClPh
542	C-Me	NEt_2	2-MeO-4-ClPh
543	C-Me	NH-3-pentyl	2-MeO-4-ClPh
544	C-Me	$NHCH(Et)CH_2CH_2OMe$	2-MeO-4-ClPh
545	C-Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-ClPh

NOTES FOR TABLE 2:

b) CI-HRMS: Calcd: 423.1355; Found: 423.1337 (M + H).

c) Analysis: Calcd: C, 61.38, H, 6.18, N, 14.32: Found: C, 61.54, H, 6.12, N, 14.37.

d) Analysis: Calcd: C: 58.02, H, 5.65, N, 14.24; Found: C, 58.11, H, 5.52, N, 14.26.

e) Analysis: Calcd: C, 59.71, H, 5.26, N, 14.85; Found: C, 59.94, H, 5.09, N, 17.23.

f) Analysis: Calcd: C, 60.48, H, 5.89, N, 14.85, Found: C, 60.62, H, 5.88, N, 14.82.

h) CI-HRMS: Calcd: 337.2388; Found: 337.2392 (M + H).

i) Analysis: Calcd: C, 68.45, H, 7.669, N, 15.21, Found: C, 68.35, H, 7.49 N, 14.91.

j) Analysis: Calcd: C, 69.08, H, 7.915, N, 14.65, Found: C, 68.85, H, 7.83, N, 14.54.

k) Analysis: Calcd: C, 73.51, H, 7.01, N, 19.48, Found: C, 71.57, H, 7.15, N, 19.12.

l) CI-HRMS: Calcd: 403.1899; Found: 403.1901 (M + H).

m) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl. 9.13; Found: C, 61.90, H, 6.66, N, 13.62, Cl, 9.25.

n) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Cl. 9.93; Found: C, 67.32, H, 6.95, N, 15.50, Cl, 9.93.

o) Analysis: Calcd: C, 74.50, H, 8.14, N, 17.38, Found: C, 74.43, H, 7.59, N, 17.16.

p) Analysis: Calcd: C, 73.10, H, 7.54, N, 19.37, Found: C, 73.18, H, 7.59, N, 18.81.

q) Analysis: Calcd: C, 73.57, H, 7.78, N, 18.65, Found: C, 73.55, H, 7.79, N, 18.64.

r) CI-HRMS: Calcd: 353.2333; Found: 353.2341 (M + H).

s) Analysis: Calcd: C, 71.56, H, 8.02, N, 15.90, Found: C, 71.45, H, 7.99, N, 15.88.

t) Analysis: Calcd: C, 65.60, H, 7.34, N, 14.57, Found: C, 65.42, H, 7.24, N, 14.37.

u) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).

v) CI-HRMS: Calcd: 399.2398; Found: 399.2396 (M + H).

w) CI-HRMS: Calcd: 383.2450; Found: 383.2447 (M + H).

x) CI-HRMS: Calcd: 403.1887; Found: 403.1901 (M + H).

y) CI-HRMS: Calcd: 295.1919; Found: 295.1923 (M + H).

z) Analysis: Calcd: C, 67.31, H, 7.06, N, 15.70, Found: C, 67.12, H, 6.86, N, 15.53.

aa) Analysis: Calcd: C, 61.77, H, 6.49, N, 14.41, Cl, 9.13; Found: C, 62.06, H, 6.37, N, 14.25, Cl, 9.12.

ab) CI-HRMS: Calcd: 337.2017; Found: 337.2028 (M + H).

ac) CI-HRMS: Calcd: 403.1893; Found: 403.1901 (M + H).

ad) Analysis: Calcd: C, 70.00, H, 7.22, N, 18.55, Found: C, 70.05, H, 7.22, N, 18.36.

ae) Analysis: Calcd: C, 70.98, H, 7.74, N, 16.55, Found: C, 71.15, H, 7.46, N, 16.56.

ag) Analysis: Calcd: C, 66.59, H, 6.76, N, 16.34,
Found: C, 66.69, H,6.82, N, 16.20.

ah) Analysis: Calcd: C, 70.38, H, 6.71, N, 18.65,
Found: C, 70.35, H,6.82, N, 18.83.

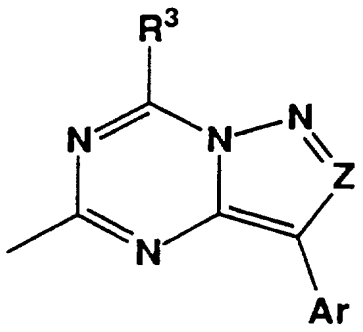
ai) Analysis: Calcd: C, 66.39, H, 5.85, N, 18.44, Cl, 9.33;
Found: C, 66.29, H, 5.51, N, 18.36, Cl, 9.31.

aj) CI-HRMS: Calcd: 369.2278; Found: 369.2291 (M + H).

ak) Analysis: Calcd: C, 64.42, H, 6.77, N, 15.02,
Found: C, 64.59, H,6.51, N, 14.81.

The examples delineated in TABLE 3 may be prepared by the methods outlined in Examples 1, 2, 3 or 6. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

TABLE 3



Ex.	Z	R_3	Ar	mp(°C)
546[a]	C-Me	$NHCH(Et)_2$	2-Me-4-Me_2N-Ph	164-166
547[b]	C-Me	S-$NHCH(CH_2CH_2OMe)$-CH_2OMe	2,4-Me2-Ph	oil
548[c]	C-Me	S-$NHCH(CH_2CH_2OMe)$-CH_2OMe	2-Me-4-Cl-Ph	oil
549[d]	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Me-4-Cl-Ph	115-116

550[e]	C-Me	NHCH(Et)CH_2CN	2-Me-4-Cl-Ph	131-132
551[f]	C-Me	$N(Et)_2$	2,3-Me_2-4-OMe-Ph	oil
552[g]	C-Me	$N(CH_2CH_2OMe)CH_2CH_2OH$	2,4-Cl_2-Ph	oil
553[h]	C-Me	$N(CH_2CH_2OMe)_2$	2,3-Me_2-4-OMe-Ph	oil
554[i]	C-Me	$NHCH(Et)_2$	2,3-Me_2-4-OMePh	123-124
555[j]	C-Me	$N(CH_2$-c-Pr)Pr	2-Me-4-Cl-Ph	oil
556[k]	C-Me	N(c-Pr)CH_2CH_2CN	2,3-Me_2-4-OMePh	158-160
557	C-Me	N(c-Pr)Et	2-Cl-4-OMePh	
558	C-Me	N(c-Pr)Me	2-Cl-4-OMePh	
559	C-Me	N(c-Pr)Pr	2-Cl-4-OMePh	
560	C-Me	N(c-Pr)Bu	2-Cl-4-OMePh	
561[l]	C-Me	$N(Et)_2$	2-Cl-4-CN-Ph	115-117
562	C-Me	$N(c\text{-}Pr)_2$	2-Cl-4-OMe	127-129
563[m]	C-Me	$NHCH(CH_2OH)_2$	2,4-Cl_2-Ph	128-129
564	C-Me	N(c-Pr)Et	2-Br-4,5-(MeO)2Ph	
565	C-Me	N(c-Pr)Me	2-Br-4,5-(MeO)2Ph	
566	C-Me	NH-c-Pr	2-Me-4-MeOPh	126-128
567	C-Me	NHCH(Et)CH2OH	2-Me-4-MeOPh	60-62
568	C-Me	NMe_2	2-Br-4,5-(MeO)2Ph	
569	C-Me	$NHCH(Et)_2$	2-Me-4-MeOPh	103-105
570	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	173-174
571	C-Me	NH-2-pentyl	2,4-Cl_2-Ph	118-120
572	C-Me	NHCH(Et)CH2CN	2,4-Cl_2-Ph	141-142
573	C-Me	NHCH(Pr)CH2OMe	2,4-Cl_2-Ph	87-88
574	C-Me	NHCH(CH2-iPr)CH2OMe	2,4-Cl_2-Ph	amorphous
575	C-Me	NH-2-butyl	2,4-Me_2-Ph	oil
576	C-Me	NH-2-pentyl	2,4-Me_2-Ph	oil
577	C-Me	NH-2-hexyl	2,4-Me_2-Ph	oil
578	C-Me	NHCH(i-Pr)Me	2,4-Me_2-Ph	oil
579	C-Me	NHCH(Me)CH2-iPr	2,4-Me_2-Ph	oil
580	C-Me	NHCH(Me)-c-C6H11	2,4-Me_2-Ph	oil
581	C-Me	NH-2-indanyl	2,4-Me_2-Ph	oil
582	C-Me	NH-1-indanyl	2,4-Me_2-Ph	oil
583	C-Me	NHCH(Me)Ph	2,4-Me_2-Ph	oil
584	C-Me	NHCH(Me)CH_2-(4-ClPh)	2,4-Me_2-Ph	oil

585	C-Me	NHCH(Me)CH_2COCH_3	2,4-Me_2-Ph	oil
586	C-Me	NHCH(Ph)CH_2Ph	2,4-Me_2-Ph	oil
587	C-Me	NHCH(Me)$(CH_2)3NEt_2$	2,4-Me_2-Ph	oil
588	C-Me	NH-(2-Ph-c-C_3H_4)	2,4-Me_2-Ph	oil
589	C-Me	NHCH(Et)CH_2CN	2,4-Me_2-Ph	119-120
590	C-Me	NH-3-hexyl	2,4-Me_2-Ph	oil
591[n]	C-Me	NEt_2	2-MeO-4-ClPh	oil
592[o]	C-Me	$NHCH(Et)_2$	2-MeO-4-ClPh	oil
593[p]	C-Me	NHCH(Et)CH_2OMe	2-MeO-4-ClPh	oil
594	C-Me	NMe_2	2-MeO-4-ClPh	oil
595[q]	C-Me	$NHCH(Et)_2$	2-OMe-4-MePh	oil
596[r]	C-Me	NEt_2	2-OMe-4-MePh	oil
597[s]	C-c-Pr	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	oil
598	C-Me	N(c-Pr)Et	2,4-Me_2-Ph	
599	C-Me	N(c-Pr)Et	2,4-Cl_2-Ph	
600	C-Me	N(c-Pr)Et	2,4,6-Me_3-Ph	
601	C-Me	N(c-Pr)Et	2-Me-4-Cl-Ph	
602	C-Me	N(c-Rr)Et	2-Cl-4-Me-Ph	
603	C-Me	$NHCH(c\text{-}Pr)_2$	2,4-Cl_2-Ph	
604	C-Me	$NHCH(c\text{-}Pr)_2$	2,4-Me_2-Ph	
605	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-Cl-Ph	
606	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-Me-Ph	
607	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-OMe-Ph	
608	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-Ph	
609	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-5-F-OMePh	
610	C-Me	NEt_2	2-Cl-5-F-OMePh	
611	C-Me	N(c-Pr)CH_2CH_2CN	2-Cl-5-F-OMePh	
612	C-Me	$NHCH(Et)_2$	2-Cl-5-F-OMePh	
613	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-5-F-OMePh	
614	C-Me	NEt_2	2,6-Me_2-pyrid-3-yl	
615	C-Me	N(c-Pr)CH_2CH_2CN	2,6-Me_2-pyrid-3-yl	
616	C-Me	$NHCH(Et)_2$	2,6-Me_2-pyrid-3-yl	
617	C-Me	$N(CH_2CH_2OMe)_2$	2,6-Me_2-pyrid-3-yl	
618	C-OH	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph	
619	C-OH	NEt_2	2,4-Me_2-Ph	
620	C-OH	N(c-Pr)CH_2CH_2CN	2,4-Me_2-Ph	

621	C-OH	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-}Ph$
623	C-OH	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
624	$C\text{-}NEt_2$	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
625	$C\text{-}NEt_2$	NEt_2	$2,4\text{-}Me_2\text{-}Ph$
626	$C\text{-}NEt_2$	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-}Ph$
627	$C\text{-}NEt_2$	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-}Ph$
628	$C\text{-}NEt_2$	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-}Ph$
629	C-Me	$NHCH(Et)_2$	2-Me-4-CN-Ph
630	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-CN-Ph

Notes for Table 3:

a) CI-HRMS: Calcd:367.2610, Found: 367.2607 (M + H);

b) CI-HRMS: Calcd:384.2400, Found: 384.2393 (M + H);

c) CI-HRMS: Calcd:404.1853, Found: 404.1844 (M + H);

d) CI-HRMS: Calcd:381.1594, Found: 381.1596 (M + H);
Analysis: Calcd: C: 63.07, H, 5.57, N, 22.07, Cl, 9.32;
Found: C: 63.40, H, 5.55, N, 21.96, Cl: 9.15

e) CI-HRMS: Calcd:369.1594, Found: 369.1576 (M + H);

f) CI-HRMS: Calcd:354.2216, Found: 354.2211 (M + H);

g) CI-HRMS: Calcd:410.1072, Found: 410.1075 (M + H);

h) CI-HRMS: Calcd:414.2427, Found: 414.2427(M + H);

i) CI-HRMS: Calcd:368.2372, Found: 368.2372(M + H);

j) CI-HRMS: Calcd:384.1955, Found: 384.1947(M + H);

k) CI-HRMS: Calcd:391.2168, Found: 391.2160(M + H);

l) CI-HRMS: Calcd:335.1984, Found: 335.1961(M + H);

m) CI-HRMS: Calcd:382.0759, Found: 382.0765(M + H);

n) NH_3-CI MS: Calcd: 360, Found: 360 (M + H)+

o) NH_3-CI MS: Calcd: 374, Found: 374 (M + H)+;
NMR ($CDCl_3$, 300 MHz) : δ 7.29 (d, J=8.4Hz, 1H), 7.04 (dd, J=1.8,8Hz, 1H), 6.96 (d, J=1.8Hz, 1H), 6.15 (d, J=10, 1H), 4.19 (m, 1H), 3.81 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.65 (m, 4H), 0.99 (t, J=7.32Hz, 6H)

p) NH_3-CI MS: Calcd: 390, Found: 390 (M + H)+;

NMR ($CDCl_3$, 300 MHz) : δ 7.28 (d, J=8Hz, 1H), 7.03 (d, J=8Hz, 1H), 6.96 (s, 1H), 6.52 (d, J=9Hz, 1H), 4.36 (m, 1H), 3.8 (s, 3H), 3.55 (m, 2H), 3.39 (s, 3H), 2.47 (s, 3H), 2.32 (s, 3H), 1.76 (m, 2H), 1.01 (t, J=7.32Hz, 3H).

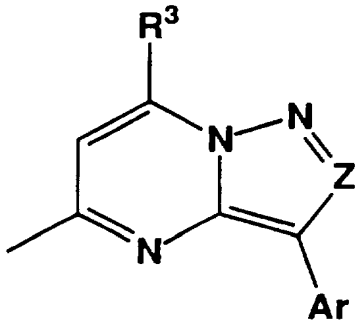
q) CI-HRMS: Calcd: 354.2294, Found: 354.2279 (M + H)+

r) CI-HRMS: Calcd: 340.2137, Found: 340.2138 (M + H)+

s) CI-HRMS: Calcd: 436.1307, Found: 436.1296 (M + H)+

The examples delineated in TABLE 4 may be prepared by the methods outlined in Examples 1A, 1B, 432, 433, 434. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, EtOAc is ethyl acetate.

TABLE 4

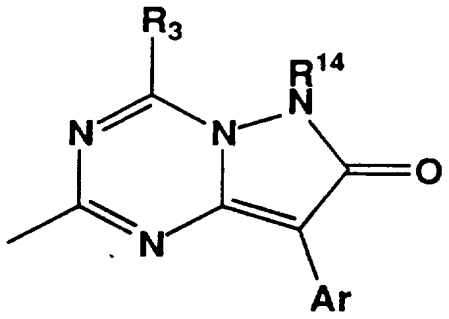


Ex.	Z	R_3	Ar	mp(°C)
631	C-Me	$NHCH(Et)_2$	2-Br-4,5-$(MeO)_2$Ph	160-161
632	C-Me	$NHCH(Et)_2$	2-Br-4-MeOPh	110-111
633	C-Me	$N(CH_2CH_2OMe)_2$	2-Br-4-MeOPh	74-76
634	C-Me	$NHCH(CH_2OMe)_2$	2-Br-4-MeOPh	128-130

	635	C-Me	$N(Et)_2$	2-Me-4-ClPh	113-114
	636	C-Me	N(c-Pr)Et	$2,4\text{-}Cl_2Ph$	
	637	C-Me	N(c-Pr)Et	$2,4\text{-}Me_2Ph$	
	638	C-Me	N(c-Pr)Et	$2,4,6\text{-}Me_3Ph$	
5	639	C-Me	N(c-Pr)Et	2-Me-4-MeOPh	
	640	C-Me	N(c-Pr)Et	2-Cl-4-MeOPh	
	641	C-Me	N(c-Pr)Et	2-Cl-4-MePh	
	642	C-Me	N(c-Pr)Et	2-Me-4-ClPh	
	643	C-Me	$NHCH(c\text{-}Pr)_2$	$2,4\text{-}Cl_2\text{-}Ph$	
10	644	C-Me	$NHCH(c\text{-}Pr)_2$	$2,4\text{-}Me_2\text{-}Ph$	
	645	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-Cl-Ph	
	646	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-Me-Ph	
	647	C-Me	$NHCH(c\text{-}Pr)_2$	2-Me-4-OMe-Ph	
	648	C-Me	$NHCH(c\text{-}Pr)_2$	2-Cl-4-OMe-Ph	
15	649	C-Me	$NHCH(CH_2OMe)_2$	2-Cl-5-F-OMePh	
	650	C-Me	NEt_2	2-Cl-5-F-OMePh	
	651	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-5-F-OMePh	
	652	C-Me	$NHCH(Et)_2$	2-Cl-5-F-OMePh	
	653	C-Me	$N(CH_2CH_2OMe)_2$	2-Cl-5-F-OMePh	
20	654	C-Me	NEt_2	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	655	C-Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	656	C-Me	$NHCH(Et)_2$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	657	C-Me	$N(CH_2CH_2OMe)_2$	$2,6\text{-}Me_2\text{-pyrid-3-yl}$	
	658	C-OH	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
25	659	C-OH	NEt_2	$2,4\text{-}Me_2\text{-Ph}$	
	660	C-OH	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-Ph}$	
	661	C-OH	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	662	C-OH	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	663	$C\text{-}NEt_2$	$NHCH(CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
30	664	$C\text{-}NEt_2$	NEt_2	$2,4\text{-}Me_2\text{-Ph}$	
	665	$C\text{-}NEt_2$	$N(c\text{-}Pr)CH_2CH_2CN$	$2,4\text{-}Me_2\text{-Ph}$	
	666	$C\text{-}NEt_2$	$NHCH(Et)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	667	$C\text{-}NEt_2$	$N(CH_2CH_2OMe)_2$	$2,4\text{-}Me_2\text{-Ph}$	
	668	C-Me	$NHCH(Et)_2$	2-Me-4-CN-Ph	
35	669	C-Me	$N(CH_2CH_2OMe)_2$	2-Me-4-CN-Ph	

The examples in Tables 5 or 6 may be prepared by the methods illustrated in Examples 1A, 1B, 2, 3, 6, 431, 432, 433, 434 or by appropriate combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example.

Table 5



Ex.	R_{14}	R_3	Ar
670	Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph
671	Me	$NHCHPr_2$	2,4-Cl_2-Ph
672	Me	NEtBu	2,4-Cl_2-Ph
673	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph
674	Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph
675	Me	NH-3-heptyl	2,4-Cl_2-Ph
676	Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph
677	Me	NEt_2	2,4-Cl_2-Ph
678	Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph
679	Me	NH-3-pentyl	2,4-Cl_2-Ph
680	Me	NMePh	2,4-Cl_2-Ph
681	Me	NPr_2	2,4-Cl_2-Ph
682	Me	NH-3-hexyl	2,4-Cl_2-Ph
683	Me	morpholino	2,4-Cl_2-Ph

684	Me	$N(CH_2Ph)CH_2CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
685	Me	$NHCH(CH_2Ph)CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
686	Me	NH-4-tetrahydropyranyl	$2,4\text{-}Cl_2\text{-}Ph$
687	Me	NH-cyclopentyl	$2,4\text{-}Cl_2\text{-}Ph$
688	Me	OEt	$2,4\text{-}Cl_2\text{-}Ph$
689	Me	$OCH(Et)CH_2OMe$	$2,4\text{-}Cl_2\text{-}Ph$
690	Me	OCH_2Ph	$2,4\text{-}Cl_2\text{-}Ph$
691	Me	O-3-pentyl	$2,4\text{-}Cl_2\text{-}Ph$
692	Me	SEt	$2,4\text{-}Cl_2\text{-}Ph$
693	Me	S(O)Et	$2,4\text{-}Cl_2\text{-}Ph$
694	Me	SO_2Et	$2,4\text{-}Cl_2\text{-}Ph$
695	Me	Ph	$2,4\text{-}Cl_2\text{-}Ph$
696	Me	$2\text{-}CF_3\text{-}Ph$	$2,4\text{-}Cl_2\text{-}Ph$
697	Me	2-Ph-Ph	$2,4\text{-}Cl_2\text{-}Ph$
698	Me	3-pentyl	$2,4\text{-}Cl_2\text{-}Ph$
699	Me	cyclobutyl	$2,4\text{-}Cl_2\text{-}Ph$
700	Me	3-pyridyl	$2,4\text{-}Cl_2\text{-}Ph$
701	Me	$CH(Et)CH_2CONMe_2$	$2,4\text{-}Cl_2\text{-}Ph$
702	Me	$CH(Et)CH_2CH_2NMe_2$	$2,4\text{-}Cl_2\text{-}Ph$
703	Me	$NHCH(CH_2OMe)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
704	Me	$NHCHPr_2$	$2,4,6\text{-}Me_3\text{-}Ph$
705	Me	NEtBu	$2,4,6\text{-}Me_3\text{-}Ph$
706	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	$2,4,6\text{-}Me_3\text{-}Ph$
707	Me	$N(CH_2CH_2OMe)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
708	Me	NH-3-heptyl	$2,4,6\text{-}Me_3\text{-}Ph$
709	Me	$NHCH(Et)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
710	Me	NEt_2	$2,4,6\text{-}Me_3\text{-}Ph$
711	Me	$NHCH(CH_2OEt)_2$	$2,4,6\text{-}Me_3\text{-}Ph$
712	Me	NH-3-pentyl	$2,4,6\text{-}Me_3\text{-}Ph$
713	Me	NMePh	$2,4,6\text{-}Me_3\text{-}Ph$
714	Me	NPr_2	$2,4,6\text{-}Me_3\text{-}Ph$
715	Me	NH-3-hexyl	$2,4,6\text{-}Me_3\text{-}Ph$
716	Me	morpholino	$2,4,6\text{-}Me_3\text{-}Ph$
717	Me	$N(CH_2Ph)CH_2CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
718	Me	$NHCH(CH_2Ph)CH_2OMe$	$2,4,6\text{-}Me_3\text{-}Ph$
719	Me	NH-4-tetrahydropyranyl	$2,4,6\text{-}Me_3\text{-}Ph$

720	Me	NH-cyclopentyl	2,4,6-Me_3-Ph
721	Me	OEt	2,4,6-Me_3-Ph
722	Me	OCH(Et)CH_2OMe	2,4,6-Me_3-Ph
723	Me	OCH_2Ph	2,4,6-Me_3-Ph
724	Me	O-3-pentyl	2,4,6-Me_3-Ph
725	Me	SEt	2,4,6-Me_3-Ph
726	Me	S(O)Et	2,4,6-Me_3-Ph
727	Me	SO_2Et	2,4,6-Me_3-Ph
728	Me	CH(CO_2Et)$_2$	2,4,6-Me_3-Ph
729	Me	C(Et)(CO_2Et)$_2$	2,4,6-Me_3-Ph
730	Me	CH(Et)CH_2OH	2,4,6-Me_3-Ph
731	Me	CH(Et)CH_2OMe	2,4,6-Me_3-Ph
732	Me	$CONMe_2$	2,4,6-Me_3-Ph
733	Me	$COCH_3$	2,4,6-Me_3-Ph
734	Me	CH(OH)CH_3	2,4,6-Me_3-Ph
735	Me	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
736	Me	Ph	2,4,6-Me_3-Ph
737	Me	2-Ph-Ph	2,4,6-Me_3-Ph
738	Me	3-pentyl	2,4,6-Me_3-Ph
739	Me	cyclobutyl	2,4,6-Me_3-Ph
740	Me	3-pyridyl	2,4,6-Me_3-Ph
741	Me	CH(Et)CH_2CONMe_2	2,4,6-Me_3-Ph
742	Me	CH(Et)$CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
743	Me	NHCH(CH_2OMe)$_2$	2,4-Me_2-Ph
744	Me	N(CH_2CH_2OMe)$_2$	2,4-Me_2-Ph
745	Me	NHCH(Et)CH_2OMe	2,4-Me_2-Ph
746	Me	NH-3-pentyl	2,4-Me_2-Ph
747	Me	NEt_2	2,4-Me_2-Ph
748	Me	N(CH_2CN)$_2$	2,4-Me_2-Ph
749	Me	NHCH(Me)CH_2OMe	2,4-Me_2-Ph
750	Me	OCH(Et)CH_2OMe	2,4-Me_2-Ph
751	Me	NPr-c-C_3H_5	2,4-Me_2-Ph
752	Me	NHCH(Me)CH_2NMe_2	2,4-Me_2-Ph
753	Me	N(c-C_3H_5)CH_2CH_2CN	2,4-Me_2-Ph
754	Me	N(Pr)CH_2CH_2CN	2,4-Me_2-Ph
755	Me	N(Bu)CH_2CH_2CN	2,4-Me_2-Ph

756	Me	$NHCHPr_2$	2,4-Me_2-Ph
757	Me	NEtBu	2,4-Me_2-Ph
758	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Me_2-Ph
759	Me	NH-3-heptyl	2,4-Me_2-Ph
760	Me	NEt_2	2,4-Me_2-Ph
761	Me	$NHCH(CH_2OEt)_2$	2,4-Me_2-Ph
762	Me	NH-3-pentyl	2,4-Me_2-Ph
763	Me	NMePh	2,4-Me_2-Ph
764	Me	NPr_2	2,4-Me_2-Ph
765	Me	NH-3-hexyl	2,4-Me_2-Ph
766	Me	morpholino	2,4-Me_2-Ph
767	Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Me_2-Ph
768	Me	$NHCH(CH_2Ph)CH_2OMe$	2,4-Me_2-Ph
769	Me	NH-4-tetrahydropyranyl	2,4-Me_2-Ph
770	Me	NH-cyclopentyl	2,4-Me_2-Ph
771	Me	$NHCH(CH_2OMe)_2$	2-Me-4-MeO-Ph
772	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-MeO-Ph
773	Me	$NHCH(Et)CH_2OMe$	2-Me-4-MeO-Ph
774	Me	$N(Pr)CH_2CH_2CN$	2-Me-4-MeO-Ph
775	Me	$OCH(Et)CH_2OMe$	2-Me-4-MeO-Ph
776	Me	$NHCH(CH_2OMe)_2$	2-Br-4-MeO-Ph
777	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-MeO-Ph
778	Me	$NHCH(Et)CH_2OMe$	2-Br-4-MeO-Ph
779	Me	$N(Pr)CH_2CH_2CN$	2-Br-4-MeO-Ph
780	Me	$OCH(Et)CH_2OMe$	2-Br-4-MeO-Ph
781	Me	$NHCH(CH_2OMe)_2$	2-Me-4-NMe_2-Ph
782	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-NMe_2-Ph
783	Me	$NHCH(Et)CH_2OMe$	2-Me-4-NMe_2-Ph
784	Me	$N(Pr)CH_2CH_2CN$	2-Me-4-NMe_2-Ph
785	Me	$OCH(Et)CH_2OMe$	2-Me-4-NMe_2-Ph
786	Me	$NHCH(CH_2OMe)_2$	2-Br-4-NMe_2-Ph
787	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-NMe_2-Ph
788	Me	$NHCH(Et)CH_2OMe$	2-Br-4-NMe_2-Ph
789	Me	$N(Pr)CH_2CH_2CN$	2-Br-4-NMe_2-Ph
790	Me	$OCH(Et)CH_2OMe$	2-Br-4-NMe_2-Ph
791	Me	$NHCH(CH_2OMe)_2$	2-Br-4-i-Pr-Ph

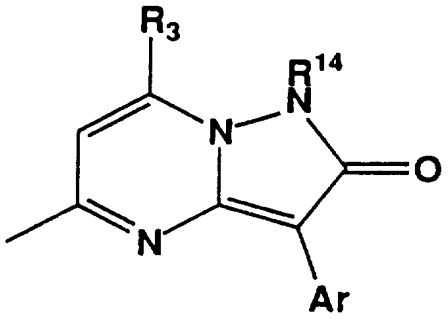
792	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-i-Pr-Ph
793	Me	NHCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
794	Me	N(Pr)CH_2CH_2CN	2-Br-4-i-Pr-Ph
795	Me	OCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
796	Me	$NHCH(CH_2OMe)_2$	2-Br-4-Me-Ph
797	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-Me-Ph
798	Me	NHCH(Et)CH_2OMe	2-Br-4-Me-Ph
799	Me	N(Pr)CH_2CH_2CN	2-Br-4-Me-Ph
800	Me	OCH(Et)CH_2OMe	2-Br-4-Me-Ph
801	Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph
802	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph
803	Me	NHCH(Et)CH_2OMe	2-Me-4-Br-Ph
804	Me	N(Pr)CH_2CH_2CN	2-Me-4-Br-Ph
805	Me	OCH(Et)CH_2OMe	2-Me-4-Br-Ph
806	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
807	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
808	Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
809	Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
810	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
811	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
812	Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph
813	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph
814	Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
815	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
816	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
817	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
818	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
819	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
820	Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph
821	Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph
822	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
823	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
824	Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph
825	Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph
826	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
827	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph

828	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
829	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
830	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
831	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
832	Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
833	Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
834	Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
835	Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
836	Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
837	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
838	Me	NEt_2	2-Br-4-MeO-Ph
839	Me	NH-3-pentyl	2-Br-4-MeO-Ph
840	Me	$NHCH(CH_2OMe)_2$	2-CN-4-Me-Ph
841	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4,6-Me_3-Ph
842	Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-Br-Ph
843	Me	$NHCH(CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
844	Me	$N(CH_2CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
845	Me	NH-3-pentyl	2,5-Me_2-4-MeO-Ph
846	Me	NEt_2	2,5-Me_2-4-MeO-Ph
847	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MePh
848	Me	$NCH(Et)CH_2OMe$	2-Cl-4-MePh
849	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh
850	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Cl-4-MePh
851	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,5-Me_2-4-MeOPh
852	Me	NEt_2	2-Me-4-MeOPh
853	Me	OEt	2-Me-4-MeOPh
854	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-MeOPh
855	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2-Me-4-MeOPh
856	Me	$NHCH(CH_2CH_2OEt)_2$	2-Me-4-MeOPh
857	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4-Cl_2-Ph
858	Me	NEt_2	2-Me-4-ClPh
859	Me	NH-3-pentyl	2-Me-4-ClPh
860	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-ClPh
861	Me	$NHCH(CH_2OMe)_2$	2-Me-4-ClPh
862	Me	NEt_2	2-Me-4-ClPh
863	Me	NEt_2	2-Cl-4-MePh

864	Me	NH-3-pentyl	2-Cl-4-MePh
865	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MeOPh
866	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
867	Me	$NHCH(Et)CH_2OMe$	2-Cl-4-MeOPh
868	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-4-MeOPh
869	Me	NEt_2	2-Cl-4-MeOPh
870	Me	NH-3-pentyl	2-Cl-4-MeOPh
871	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4-MeOPh
872	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4-MeOPh
873	Me	$NHCH(Et)CH_2CH_2OMe$	2-Br-4-MeOPh
874	Me	$NHCH(Me)CH_2CH_2OMe$	2-Br-4-MeOPh
875	Me	$NHCH(Et)CH_2CH_2OMe$	2-Me-4-MeOPh
876	Me	$NHCH(Me)CH_2CH_2OMe$	2-Me-4-MeOPh
877	Me	$NHCH(CH_2OMe)_2$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
878	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
879	Me	$NHCH(Et)CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
880	Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
881	Me	NEt_2	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
882	Me	NH-3-pentyl	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
883	Me	$NHCH(Et)CH_2CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
884	Me	$NHCH(Me)CH_2CH_2OMe$	$2\text{-Cl-4,5-(MeO)}_2\text{Ph}$
885	Me	$NHCH(CH_2OMe)_2$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
886	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
887	Me	$NHCH(Et)CH_2OMe$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
888	Me	$N(c\text{-}Pr)CH_2CH_2CN$	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
889	Me	NEt_2	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
890	Me	NH-3-pentyl	$2\text{-Br-4,5-(MeO)}_2\text{Ph}$
891	Me	$NHCH(CH_2OMe)_2$	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
892	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
893	Me	NEt_2	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
894	Me	NH-3-pentyl	$2\text{-Cl-4,6-(MeO)}_2\text{Ph}$
895	Me	$NHCH(CH_2OMe)_2$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
896	Me	$N(CH_2CH_2OMe)_2$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
897	Me	$NHCH(Et)CH_2OMe$	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
898	Me	NEt_2	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$
899	Me	NH-3-pentyl	$2\text{-Me-4,6-(MeO)}_2\text{Ph}$

	900	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
	901	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
	902	Me	NHCH(CH_2OMe)$_2$	2-Me0-4-MePh
	903	Me	N(CH_2CH_2OMe)$_2$	2-Me0-4-MePh
	904	Me	NHCH(Et)CH_2OMe	2-Me0-4-MePh
	905	Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-MePh
	906	Me	NEt_2	2-Me0-4-MePh
	907	Me	NH-3-pentyl	2-Me0-4-MePh
	908	Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-MePh
	909	Me	NHCH(Me)CH_2CH_2OMe	2-Me0-4-MePh
	910	Me	NHCH(CH_2OMe)$_2$	2-Me0-4-MePh
	911	Me	N(CH_2CH_2OMe)$_2$	2-Me0-4-MePh
	912	Me	NHCH(Et)CH_2OMe	2-Me0-4-MePh
	913	Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-MePh
	914	Me	NEt_2	2-Me0-4-MePh
	915	Me	NH-3-pentyl	2-Me0-4-MePh
	916	Me	NHCH(CH_2OMe)$_2$	2-Me0-4-ClPh
	917	Me	N(CH_2CH_2OMe)$_2$	2-Me0-4-ClPh
	918	Me	NHCH(Et)CH_2OMe	2-Me0-4-ClPh
	919	Me	NEt_2	2-Me0-4-ClPh
	920	Me	NH-3-pentyl	2-Me0-4-ClPh

Table 6



Ex.	R_{14}	R_3	Ar
921	Me	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph
922	Me	$NHCHPr_2$	2,4-Cl_2-Ph
923	Me	NEtBu	2,4-Cl_2-Ph
924	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Cl_2-Ph
925	Me	$N(CH_2CH_2OMe)_2$	2,4-Cl_2-Ph
926	Me	NH-3-heptyl	2,4-Cl_2-Ph
927	Me	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph
928	Me	NEt_2	2,4-Cl_2-Ph
929	Me	$NHCH(CH_2OEt)_2$	2,4-Cl_2-Ph
930	Me	NH-3-pentyl	2,4-Cl_2-Ph
931	Me	NMePh	2,4-Cl_2-Ph
932	Me	NPr_2	2,4-Cl_2-Ph
933	Me	NH-3-hexyl	2,4-Cl_2-Ph
934	Me	morpholino	2,4-Cl_2-Ph
935	Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4-Cl_2-Ph
936	Me	$NHCH(CH_2Ph)CH_2OMe$	2,4-Cl_2-Ph
937	Me	NH-4-tetrahydropyranyl	2,4-Cl_2-Ph
938	Me	NH-cyclopentyl	2,4-Cl_2-Ph
939	Me	OEt	2,4-Cl_2-Ph
940	Me	$OCH(Et)CH_2OMe$	2,4-Cl_2-Ph
941	Me	OCH_2Ph	2,4-Cl_2-Ph
942	Me	O-3-pentyl	2,4-Cl_2-Ph
943	Me	SEt	2,4-Cl_2-Ph

944	Me	S(O)Et	2,4-Cl_2-Ph
945	Me	SO_2Et	2,4-Cl_2-Ph
946	Me	Ph	2,4-Cl_2-Ph
947	Me	2-CF_3-Ph	2,4-Cl_2-Ph
948	Me	2-Ph-Ph	2,4-Cl_2-Ph
949	Me	3-pentyl	2,4-Cl_2-Ph
950	Me	cyclobutyl	2,4-Cl_2-Ph
951	Me	3-pyridyl	2,4-Cl_2-Ph
952	Me	$CH(Et)CH_2CONMe_2$	2,4-Cl_2-Ph
953	Me	$CH(Et)CH_2CH_2NMe_2$	2,4-Cl_2-Ph
954	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-Ph
955	Me	$NHCHPr_2$	2,4,6-Me_3-Ph
956	Me	NEtBu	2,4,6-Me_3-Ph
957	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4,6-Me_3-Ph
958	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-Ph
959	Me	NH-3-heptyl	2,4,6-Me_3-Ph
960	Me	$NHCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
961	Me	NEt_2	2,4,6-Me_3-Ph
962	Me	$NHCH(CH_2OEt)_2$	2,4,6-Me_3-Ph
963	Me	NH-3-pentyl	2,4,6-Me_3-Ph
964	Me	NMePh	2,4,6-Me_3-Ph
965	Me	NPr_2	2,4,6-Me_3-Ph
966	Me	NH-3-hexyl	2,4,6-Me_3-Ph
967	Me	morpholino	2,4,6-Me_3-Ph
968	Me	$N(CH_2Ph)CH_2CH_2OMe$	2,4,6-Me_3-Ph
969	Me	$NHCH(CH_2Ph)CH_2OMe$	2,4,6-Me_3-Ph
970	Me	NH-4-tetrahydropyranyl	2,4,6-Me_3-Ph
971	Me	NH-cyclopentyl	2,4,6-Me_3-Ph
972	Me	OEt	2,4,6-Me_3-Ph
973	Me	$OCH(Et)CH_2OMe$	2,4,6-Me_3-Ph
974	Me	OCH_2Ph	2,4,6-Me_3-Ph
975	Me	O-3-pentyl	2,4,6-Me_3-Ph
976	Me	SEt	2,4,6-Me_3-Ph
977	Me	S(O)Et	2,4,6-Me_3-Ph
978	Me	SO_2Et	2,4,6-Me_3-Ph
979	Me	$CH(CO_2Et)_2$	2,4,6-Me_3-Ph

	980	Me	$C(Et)(CO_2Et)_2$	2,4,6-Me_3-Ph
	981	Me	$CH(Et)CH_2OH$	2,4,6-Me_3-Ph
	982	Me	$CH(Et)CH_2OMe$	2,4,6-Me_3-Ph
	983	Me	$CONMe_2$	2,4,6-Me_3-Ph
5	984	Me	$COCH_3$	2,4,6-Me_3-Ph
	985	Me	$CH(OH)CH_3$	2,4,6-Me_3-Ph
	986	Me	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
	987	Me	Ph	2,4,6-Me_3-Ph
	988	Me	2-Ph-Ph	2,4,6-Me_3-Ph
10	989	Me	3-pentyl	2,4,6-Me_3-Ph
	990	Me	cyclobutyl	2,4,6-Me_3-Ph
	991	Me	3-pyridyl	2,4,6-Me_3-Ph
	992	Me	$CH(Et)CH_2CONMe_2$	2,4,6-Me_3-Ph
	993	Me	$CH(Et)CH_2CH_2NMe_2$	2,4,6-Me_3-Ph
15	994	Me	$NHCH(CH_2OMe)_2$	2,4-Me_2-Ph
	995	Me	$N(CH_2CH_2OMe)_2$	2,4-Me_2-Ph
	996	Me	$NHCH(Et)CH_2OMe$	2,4-Me_2-Ph
	997	Me	NH-3-pentyl	2,4-Me_2-Ph
	998	Me	NEt_2	2,4-Me_2-Ph
20	999	Me	$N(CH_2CN)_2$	2,4-Me_2-Ph
	1000	Me	$NHCH(Me)CH_2OMe$	2,4-Me_2-Ph
	1001	Me	$OCH(Et)CH_2OMe$	2,4-Me_2-Ph
	1002	Me	$NPr\text{-}c\text{-}C_3H_5$	2,4-Me_2-Ph
	1003	Me	$NHCH(Me)CH_2NMe_2$	2,4-Me_2-Ph
25	1004	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4-Me_2-Ph
	1005	Me	$N(Pr)CH_2CH_2CN$	2,4-Me_2-Ph
	1006	Me	$N(Bu)CH_2CH_2CN$	2,4-Me_2-Ph
	1007	Me	$NHCHPr_2$	2,4-Me_2-Ph
	1008	Me	NEtBu	2,4-Me_2-Ph
30	1009	Me	$NPr(CH_2\text{-}c\text{-}C_3H_5)$	2,4-Me_2-Ph
	1010	Me	NH-3-heptyl	2,4-Me_2-Ph
	1011	Me	NEt_2	2,4-Me_2-Ph
	1012	Me	$NHCH(CH_2OEt)_2$	2,4-Me_2-Ph
	1013	Me	NH-3-pentyl	2,4-Me_2-Ph
35	1014	Me	NMePh	2,4-Me_2-Ph
	1015	Me	NPr_2	2,4-Me_2-Ph

1016	Me	NH-3-hexyl	2,4-Me_2-Ph
1017	Me	morpholino	2,4-Me_2-Ph
1018	Me	N(CH_2Ph)CH_2CH_2OMe	2,4-Me_2-Ph
1019	Me	NHCH(CH_2Ph)CH_2OMe	2,4-Me_2-Ph
1020	Me	NH-4-tetrahydropyranyl	2,4-Me_2-Ph
1021	Me	NH-cyclopentyl	2,4-Me_2-Ph
1022	Me	NHCH(CH_2OMe)$_2$	2-Me-4-MeO-Ph
1023	Me	N(CH_2CH_2OMe)$_2$	2-Me-4-MeO-Ph
1024	Me	NHCH(Et)CH_2OMe	2-Me-4-MeO-Ph
1025	Me	N(Pr)CH_2CH_2CN	2-Me-4-MeO-Ph
1026	Me	OCH(Et)CH_2OMe	2-Me-4-MeO-Ph
1027	Me	NHCH(CH_2OMe)$_2$	2-Br-4-MeO-Ph
1028	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-MeO-Ph
1029	Me	NHCH(Et)CH_2OMe	2-Br-4-MeO-Ph
1030	Me	N(Pr)CH_2CH_2CN	2-Br-4-MeO-Ph
1031	Me	OCH(Et)CH_2OMe	2-Br-4-MeO-Ph
1032	Me	NHCH(CH_2OMe)$_2$	2-Me-4-NMe_2-Ph
1033	Me	N(CH_2CH_2OMe)$_2$	2-Me-4-NMe_2-Ph
1034	Me	NHCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph
1035	Me	N(Pr)CH_2CH_2CN	2-Me-4-NMe_2-Ph
1036	Me	OCH(Et)CH_2OMe	2-Me-4-NMe_2-Ph
1037	Me	NHCH(CH_2OMe)$_2$	2-Br-4-NMe_2-Ph
1038	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-NMe_2-Ph
1039	Me	NHCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph
1040	Me	N(Pr)CH_2CH_2CN	2-Br-4-NMe_2-Ph
1041	Me	OCH(Et)CH_2OMe	2-Br-4-NMe_2-Ph
1042	Me	NHCH(CH_2OMe)$_2$	2-Br-4-i-Pr-Ph
1043	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-i-Pr-Ph
1044	Me	NHCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
1045	Me	N(Pr)CH_2CH_2CN	2-Br-4-i-Pr-Ph
1046	Me	OCH(Et)CH_2OMe	2-Br-4-i-Pr-Ph
1047	Me	NHCH(CH_2OMe)$_2$	2-Br-4-Me-Ph
1048	Me	N(CH_2CH_2OMe)$_2$	2-Br-4-Me-Ph
1049	Me	NHCH(Et)CH_2OMe	2-Br-4-Me-Ph
1050	Me	N(Pr)CH_2CH_2CN	2-Br-4-Me-Ph
1051	Me	OCH(Et)CH_2OMe	2-Br-4-Me-Ph

1052	Me	$NHCH(CH_2OMe)_2$	2-Me-4-Br-Ph
1053	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-Br-Ph
1054	Me	$NHCH(Et)CH_2OMe$	2-Me-4-Br-Ph
1055	Me	$N(Pr)CH_2CH_2CN$	2-Me-4-Br-Ph
1056	Me	$OCH(Et)CH_2OMe$	2-Me-4-Br-Ph
1057	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
1058	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-Me_2-Ph
1059	Me	$NHCH(CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
1060	Me	$N(CH_2CH_2OMe)_2$	4-Br-2,6-$(Me)_2$-Ph
1061	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1062	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1063	Me	$NHCH(CH_2OMe)_2$	2-Br-4-CF_3-Ph
1064	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-CF_3-Ph
1065	Me	$NHCH(CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
1066	Me	$N(CH_2CH_2OMe)_2$	2-Br-4,6-$(MeO)_2$-Ph
1067	Me	$NHCH(CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
1068	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$-Ph
1069	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1070	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1071	Me	$NHCH(CH_2OMe)_2$	4-(COMe)-2-Br-Ph
1072	Me	$N(CH_2CH_2OMe)_2$	4-(COMe)-2-Br-Ph
1073	Me	$NHCH(CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
1074	Me	$N(CH_2CH_2OMe)_2$	2,4,6-Me_3-pyrid-3-yl
1075	Me	$NHCH(CH_2OMe)_2$	2,4-$(Br)_2$-Ph
1076	Me	$N(CH_2CH_2OMe)_2$	2,4-$(Br)_2$-Ph
1077	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1078	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SMe-Ph
1079	Me	$NHCH(CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
1080	Me	$N(CH_2CH_2OMe)_2$	4-i-Pr-2-SO_2Me-Ph
1081	Me	$NHCH(CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1082	Me	$N(CH_2CH_2OMe)_2$	2,6-$(Me)_2$-4-SMe-Ph
1083	Me	$NHCH(CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
1084	Me	$N(CH_2CH_2OMe)_2$	2,6-(Me)2-4-SO_2Me-Ph
1085	Me	$NHCH(CH_2OMe)_2$	2-I-4-i-Pr-Ph
1086	Me	$N(CH_2CH_2OMe)_2$	2-I-4-i-Pr-Ph
1087	Me	$NHCH(CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph

1088	Me	$N(CH_2CH_2OMe)_2$	2-Br-4-$N(Me)_2$-6-MeO-Ph
1089	Me	NEt_2	2-Br-4-MeO-Ph
1090	Me	NH-3-pentyl	2-Br-4-MeO-Ph
1091	Me	$NHCH(CH_2OMe)_2$	2-CN-4-Me-Ph
1092	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4,6-Me_3-Ph
1093	Me	$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-Br-Ph
1094	Me	$NHCH(CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
1095	Me	$N(CH_2CH_2OMe)_2$	2,5-Me_2-4-MeO-Ph
1096	Me	NH-3-pentyl	2,5-Me_2-4-MeO-Ph
1097	Me	NEt_2	2,5-Me_2-4-MeO-Ph
1098	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MePh
1099	Me	$NCH(Et)CH_2OMe$	2-Cl-4-MePh
1100	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MePh
1101	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Cl-4-MePh
1102	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,5-Me_2-4-MeOPh
1103	Me	NEt_2	2-Me-4-MeOPh
1104	Me	OEt	2-Me-4-MeOPh
1105	Me	(S)-$NHCH(CH_2CH_2OMe)CH_2OMe$	2-Me-4-MeOPh
1106	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2-Me-4-MeOPh
1107	Me	$NHCH(CH_2CH_2OEt)_2$	2-Me-4-MeOPh
1108	Me	$N(c\text{-}C_3H_5)CH_2CH_2CN$	2,4-Cl_2-Ph
1109	Me	NEt_2	2-Me-4-ClPh
1110	Me	NH-3-pentyl	2-Me-4-ClPh
1111	Me	$N(CH_2CH_2OMe)_2$	2-Me-4-ClPh
1112	Me	$NHCH(CH_2OMe)_2$	2-Me-4-ClPh
1113	Me	NEt_2	2-Me-4-ClPh
1114	Me	NEt_2	2-Cl-4-MePh
1115	Me	NH-3-pentyl	2-Cl-4-MePh
1116	Me	$NHCH(CH_2OMe)_2$	2-Cl-4-MeOPh
1117	Me	$N(CH_2CH_2OMe)_2$	2-Cl-4-MeOPh
1118	Me	$NHCH(Et)CH_2OMe$	2-Cl-4-MeOPh
1119	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-Cl-4-MeOPh
1120	Me	NEt_2	2-Cl-4-MeOPh
1121	Me	NH-3-pentyl	2-Cl-4-MeOPh
1123	Me	$NHCH(Et)CH_2CH_2OMe$	2-Cl-4-MeOPh
1124	Me	$NHCH(Me)CH_2CH_2OMe$	2-Cl-4-MeOPh

1125	Me	NHCH(Et)CH_2CH_2OMe	2-Br-4-MeOPh
1126	Me	NHCH(Me)CH_2CH_2OMe	2-Br-4-MeOPh
1127	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
1128	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
1129	Me	NHCH($CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
1130	Me	N($CH_2CH_2OMe)_2$	2-Cl-4,5-$(MeO)_2$Ph
1131	Me	NHCH(Et)CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1132	Me	N(c-Pr)CH_2CH_2CN	2-Cl-4,5-$(MeO)_2$Ph
1133	Me	NEt_2	2-Cl-4,5-$(MeO)_2$Ph
1134	Me	NH-3-pentyl	2-Cl-4,5-$(MeO)_2$Ph
1135	Me	NHCH(Et)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1136	Me	NHCH(Me)CH_2CH_2OMe	2-Cl-4,5-$(MeO)_2$Ph
1137	Me	NHCH($CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
1138	Me	N($CH_2CH_2OMe)_2$	2-Br-4,5-$(MeO)_2$Ph
1139	Me	NHCH(Et)CH_2OMe	2-Br-4,5-$(MeO)_2$Ph
1140	Me	N(c-Pr)CH_2CH_2CN	2-Br-4,5-$(MeO)_2$Ph
1141	Me	NEt_2	2-Br-4,5-$(MeO)_2$Ph
1142	Me	NH-3-pentyl	2-Br-4,5-$(MeO)_2$Ph
1143	Me	NHCH($CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
1144	Me	N($CH_2CH_2OMe)_2$	2-Cl-4,6-$(MeO)_2$Ph
1145	Me	NEt_2	2-Cl-4,6-$(MeO)_2$Ph
1146	Me	NH-3-pentyl	2-Cl-4,6-$(MeO)_2$Ph
1147	Me	NHCH($CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
1148	Me	N($CH_2CH_2OMe)_2$	2-Me-4,6-$(MeO)_2$Ph
1149	Me	NHCH(Et)CH_2OMe	2-Me-4,6-$(MeO)_2$Ph
1150	Me	NEt_2	2-Me-4,6-$(MeO)_2$Ph
1151	Me	NH-3-pentyl	2-Me-4,6-$(MeO)_2$Ph
1152	Me	NHCH(Et)CH_2CH_2OMe	2-Me-4-MeOPh
1153	Me	NHCH(Me)CH_2CH_2OMe	2-Me-4-MeOPh
1154	Me	NHCH($CH_2OMe)_2$	2-Me0-4-MePh
1155	Me	N($CH_2CH_2OMe)_2$	2-Me0-4-MePh
1156	Me	NHCH(Et)CH_2OMe	2-Me0-4-MePh
1157	Me	N(c-Pr)CH_2CH_2CN	2-Me0-4-MePh
1158	Me	NEt_2	2-Me0-4-MePh
1159	Me	NH-3-pentyl	2-Me0-4-MePh
1160	Me	NHCH(Et)CH_2CH_2OMe	2-Me0-4-MePh

1161	Me	$NHCH(Me)CH_2CH_2OMe$	2-MeO-4-MePh
1162	Me	$NHCH(CH_2OMe)_2$	2-MeO-4-MePh
1163	Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-MePh
1164	Me	$NHCH(Et)CH_2OMe$	2-MeO-4-MePh
1165	Me	$N(c\text{-}Pr)CH_2CH_2CN$	2-MeO-4-MePh
1166	Me	NEt_2	2-MeO-4-MePh
1167	Me	NH-3-pentyl	2-MeO-4-MePh
1168	Me	$NHCH(CH_2OMe)_2$	2-MeO-4-ClPh
1169	Me	$N(CH_2CH_2OMe)_2$	2-MeO-4-ClPh
1170	Me	$NHCH(Et)CH_2OMe$	2-MeO-4-ClPh
1171	Me	NEt_2	2-MeO-4-ClPh
1172	Me	NH-3-pentyl	2-MeO-4-ClPh

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a

hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 μM hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1 x 10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μg/l aprotinin, 1 μg/ml leupeptin and 1 μg/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 μg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 μl capacity. To each well is added 50 μl of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 μl of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 μl of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I-o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND

[P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (**1980**), which provides Ki values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6m}) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the

Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**). Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10

mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for

parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was

100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

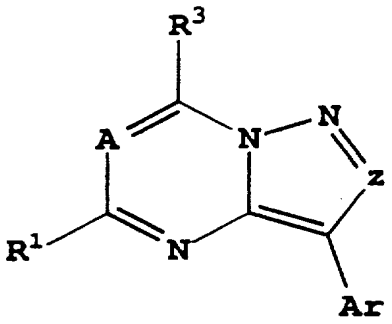
The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

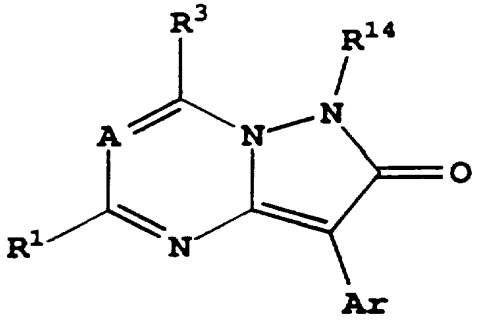
CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and

pharmaceutically acceptable salt or pro-drug forms thereof, wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from:

C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-

C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5

substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

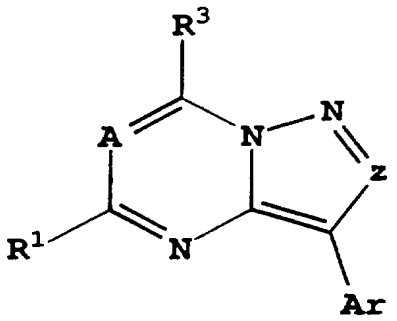
heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

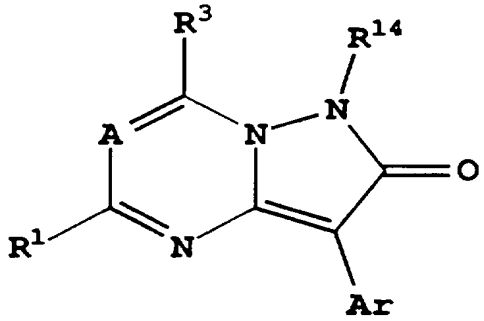
2. A method of claim 1 wherein, in the compound of Formulae (1) or (2), Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

3. A method of claim 1 wherein, in the compound of Formulae (1) or (2), A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

4. A compound of Formulae (1) or (2):



(1)



(2)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein:

A is N or CR;

Z is N or CR^2;

Ar is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each Ar optionally substituted with 1 to 5 R^4 groups and each Ar is attached to an unsaturated carbon atom;

R is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl;

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl,

halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^3 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $OC(O)R^{13}$, NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$, NR^6R^7, $NR^{6a}R^{7a}$, $N(OR^7)R^6$, $CONR^6R^7$, aryl, heteroaryl and heterocyclyl, or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^4 is independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7,

or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^6 and R^7, R^{6a} and R^{7a} are independently selected at each occurrence from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{14} is selected from C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_3-C_8 cycloalkyl, or C_4-C_{12} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, and C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl and C_1-C_6 alkylsulfonyl;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano,

OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, -COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2,

with the provisos that:

(1) when A is N, Z is CR^2, R^2 is H, R^3 is $-OR^7$ or $-OCOR^{13}$, and R^7 is H, then R^1 is not H, OH or SH;

(2) when A is N, Z is CR^2, R^1 is CH_3 or C_2H_5, R^2 is H, and R^3 is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, then Ar is not phenyl or m-CH_3-phenyl;

(3) when A is N, Z is CR^2, R^2 is H, and Ar is pyridyl, pyrimidinyl or pyrazinyl, and R^3 is $NR^{6a}R^{7a}$, then R^{6a} and R^{7a} are not H or alkyl;

(4) when A is N, Z is CR^2, and R^2 is $SO_2NR^6R^7$, then R^3 is not OH or SH;

(5) when A is CR and Z is CR^2, then R^2 is not-$NR^6SO_2R^7$ or -$SO_2NR^6R^7$;

(6) when A is N, Z is CR^2 and R^2 is -$NR^6SO_2R^7$ or -$SO_2NR^6R^7$, then R^3 is not OH or SH;

(7) when A is N, Z is CR^2, R^1 is methyl or ethyl, R^2 is H, and R^3 is H, OH, CH_3, C_2H_5, C_6H_5, n-C_3H_7, iso-C_3H_7, SH, SCH_3, NH(n-C_4H_9), or $N(C_2H_5)_2$, then Ar is not unsubstituted phenyl or m-methylphenyl;

(8) when A is CR, Z is CR^2, R^2 is H, phenyl or alkyl, R^3 is NR^8COR^7 and Ar is phenyl or phenyl substituted with phenylthio, then R^7 is not aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocycly(C_1-C_4 alkyl);

(9) when A is CR, Z is CR^2, R^2 is H or alkyl, Ar is phenyl, and R^3 is SR^{13} or $NR^{6a}R^{7a}$, then R^{13} is not aryl or heteroaryl and R^{6a} and R^{7a} are not H or aryl; or

(10) when A is CH, Z is CR^2, R^1 is OR^{11}, R^2 is H, R^3 is OR^7, and R^7 and R^{11} are both H, then Ar is not

phenyl, p-Br-phenyl, p-Cl-phenyl, p-$NHCOCH_3$-phenyl, p-CH_3-phenyl, pyridyl or naphthyl;

(11) when A is CH, Z is CR^2, R^2 is H, Ar is unsubstituted phenyl, and R^3 is CH_3, C_2H_5, CF_3 or C_6H_4F, then R_1 is not CF_3 or C_2F_5;

(12) when A is CR, R is H, Z is CR^2, R^2 is OH, and R^1 and R^3 are H, then Ar is not phenyl;

(13) when A is CR, R is H, Z is CR^2, R^2 is OH or NH_2, R^1 and R^3 are CH_3, then Ar is not 4-phenyl-3-cyano-2-aminopyrid-2-yl.

5. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof with the additional provisos that: (1) when A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1$-C_4 alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{6a} is unsubstituted C_1-C_4 alkyl, then R^{7a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl; and (2) A is N, R^1 is H, C_1-C_4 alkyl, halo, CN, C_1-C_{12} hydroxyalkyl, C_1-C_4 alkoxyalkyl or $SO_2(C_1$-C_4 alkyl), R^3 is $NR^{6a}R^{7a}$ and R^{7a} is unsubstituted C_1-C_4 alkyl, then R^{6a} is not phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, indolyl or C_3-C_6 cycloalkyl.

6. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, each optionally substituted with 1 to 4 R^4 substituents.

7. A compound of claim 6 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N, Z is CR^2, Ar is 2,4-dichlorophenyl, 2,4-dimethylphenyl or 2,4,6-trimethylphenyl, R^1 and R^2 are CH_3, and R^3 is $NR^{6a}R^{7a}$.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 4.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 6.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 7.

11. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein A is N.

12. A compound of Formula (2) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

13. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

14. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

15. A compound of claim 12 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

16. A compound of Formula (1) of claim 11 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

17. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

18. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

19. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl)-, heterocyclyl or heterocyclyl(C_1-C_4 alkyl)-; and

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-

C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

20. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

21. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is selected from:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

22. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15},

CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

23. A compound of claim 18 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

24. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

25. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

26. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

27. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

28. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

29. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

30. A compound of claim 24 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

31. A compound of claim 16 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

32. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is independently selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl)-, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is independently selected at each occurrence from:

-H,

-C_5-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each

occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl),

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups.

33. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are selected from:

-C_1-C_4 alkyl or C_3-C_6 cycloalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, -COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, N(COR15)2, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl, and

-aryl or heteroaryl.

34. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are identical and are

-C_1-C_4 alkyl, each such C_1-C_4 alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

35. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} is selected from:

-H,

-C_1-C_{10} alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

R^{7a} is:

-C_1-C_4 alkyl and each such C_1-C_4 alkyl is substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4

haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

36. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein one of R^{6a} and R^{7a} is selected from:

-C_3-C_6 cycloalkyl, each such C_3-C_6 cycloalkyl optionally substituted with 1-3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl,

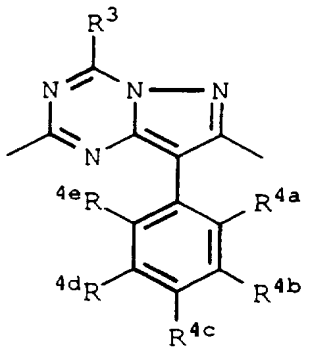
-heteroaryl or

-heterocyclyl,

and the other of R^{6a} and R^{7a} is unsubstituted C_1-C_4 alkyl.

37. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, each such C_1-C_{10} alkyl optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

38. A compound of claim 31 of Formula (50)



FORMULA (50)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, selected from the group consisting of:

a compound of Formula (50) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-(n\text{-}Pr)(CH_2cPr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Bu)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Me)(Ph)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(n\text{-}Pr)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(n\text{-}Pr)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -OEt, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CN)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-OCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Pr)(CH_2cPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Me)(CH_2N(Me)_2)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(cPr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(n-Bu)(CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OEt)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2CH_2OMe)(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is morpholino, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(c\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is CN, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is Me;

a compound of Formula (50) wherein R^3 is $-NCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is Me and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NH(CH_2OMe)(CH_2-iPr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is H, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(CH_2CH_2OMe)2, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(n-Pr), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OEt)(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OMe)(CH_2CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is NMe2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(Et)2, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Br, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is NMe_2, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is (*S*)-$NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(CH_2OMe)(CH_2CH_2OMe)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NH(Et)(CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)(CH_2CH_2OH)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2c\text{-}Pr)(n\text{-}Pr)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is Me, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-NHCH(Et)(CH_2OMe)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is CN, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (50) wherein R^3 is -NHCH(CH_2OH)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (50) wherein R^3 is N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H

a compound of Formula (51) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H.

39. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

40. A compound of claim 31 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 4-(bis-(2-methoxyethyl)amino)-2,7-dimethyl-8-(2,5-dimethyl-4-methoxyphenyl)-[1,5-a]-pyrazolo-1,3,5-triazine.

41. A compound of claim 4 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically

acceptable salt or pro-drug forms thereof wherein A is CR.

42. A compound of Formula (2) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

43. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

44. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

45. A compound of claim 42 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

46. A compound of Formula (1) of claim 41 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Z is CR^2.

47. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl and each Ar is optionally substituted with 1 to 4 R^4 substituents.

48. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^3 is $NR^{6a}R^{7a}$ or OR^7.

49. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents, and R^3 is $NR^{6a}R^{7a}$ or OR^7.

50. A compound of claim 49 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

51. A compound of claim 46 and isomers thereof, stereoisomeric forms thereof, or mixtures of

stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein

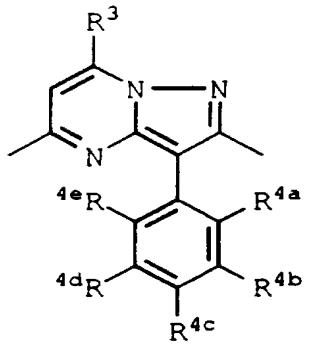
-Ar is phenyl, pyridyl or 2,3-dihydrobenzofuranyl, and each Ar is optionally substituted with 1 to 4 R^4 substituents,

-R^3 is $NR^{6a}R^{7a}$ or OR^7 and

-R^1 and R^2 are independently selected from H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl.

52. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof wherein R^{6a} and R^{7a} are independently H or C_1-C_{10} alkyl, and each such C_1-C_{10} alkyl is optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $R^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl.

53. A compound of claim 51 of Formula (51)



FORMULA (51)

and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof selected from the group consisting of:

a compound of Formula (51) wherein R^3 is $-NHCH(n\text{-}Pr)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(c\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(n\text{-}Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(n\text{-}Bu)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(Et)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(CH_2CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(Et), R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(n-Pr)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH(CH_2OMe)$_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NH(CH_2CH_2OMe)CH_2OMe, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(n-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is (*S*) $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NH(CH_2CH_2OMe)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -N(c-Pr)(CH_2CH_2CN), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH (n-Pr)(CH_2OMe), R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is -NHCH (n-Pr)(CH_2OMe), R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Br, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is OMe, R^{4d} is OMe and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(CH_2CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(CH_2OMe)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-N(Bu)(Et)$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)CH_2OMe$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Cl, R^{4b} is H, R^{4c} is Me, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NHCH(Et)_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is Cl, R^{4d} is H and R^{4e} is H;

a compound of Formula (51) wherein R^3 is $-NEt_2$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H; and

a compound of Formula (51) wherein R^3 is $-N(Pr)(CH_2CH_2CN)$, R^{4a} is Me, R^{4b} is H, R^{4c} is OMe, R^{4d} is H and R^{4e} is H.

54. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(3-pentylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine.

55. A compound of claim 51 and and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(Diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl-[1,5-a]-pyrazolopyrimidine.

56. A compound of claim 51 and isomers thereof, stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof, wherein said compound is 7-(N-(3-cyanopropyl)-N-propylamino)-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

57. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 4.

58. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 24.

59. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 38.

60. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 39.

61. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 40.

62. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 53.

63. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 54.

64. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 55.

65. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 56.

66. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility

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problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 4.

67. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 24.

68. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or

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alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 38.

69. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 39.

70. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's

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disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 40.

71. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 53.

72. A method of treating affective disorder, anxiety, depression, headache, irritable bowel

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syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 54.

73. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 55.

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74. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of claim 56.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/13072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/505 //(C07D487/04,239:00,231:00), (C07D487/04,251:00,231:00),(C07D487/04,249:00,239:00), (C07D487/04,251:00,249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 591 528 A (OTSUKA PHARMA CO LTD) 13 April 1994 cited in the application see the whole document ---	1-76
X	EP 0 531 901 A (FUJISAWA PHARMACEUTICAL CO) 17 March 1993 cited in the application see the whole document --- -/--	1-76

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1997	23. 12. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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INTERNATIONAL SEARCH REPORT

Inter. ɔnal Application No
PCT/US 97/13072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Inter. ɔnal Application No
PCT/US 97/13072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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E	WO 97 29109 A (JANSSEN PHARMACEUTICA NV ;NEUROCRINE BIOSCIENCES INC (US); CHEN CH) 14 August 1997 see the whole document	1-76

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 July 2005 (14.07.2005)

PCT

(10) International Publication Number
WO 2005/063755 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/495

(21) International Application Number: PCT/IB2004/004234

(22) International Filing Date: 20 December 2004 (20.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/532,031 22 December 2003 (22.12.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

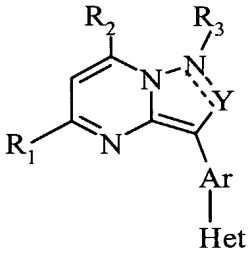
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/063755 A1

(54) Title: CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO



(I)

(57) Abstract: CRF receptor antagonists are disclosed which have utility in the treatment of a variety of disorders, including the treatment of disorders manifesting hypersecretion of CRF in a warm-blooded animals, such as stroke. The CRF receptor antagonists of this invention have the following structure (I), including stereoisomers, prodrugs and pharmaceutically acceptable salts thereof, wherein R1, R2, R3, Y, Ar, and Het are as defined herein. Compositions containing a CRF receptor antagonist in combination with a pharmaceutically acceptable carrier are also disclosed, as well as methods for use of the same.

CRF RECEPTOR ANTAGONISTS AND METHODS RELATING THERETO

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial No. 60/532,031, filed December 12, 2003, the entire disclosure of which is incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates generally to CRF receptor antagonists and to methods of treating disorders by administration of such antagonists to a mammal in need thereof.

BACKGROUND OF THE INVENTION

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide (Vale et al., *Science 213*:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA 80*:4851, 1983; Shibahara et al., *EMBO J. 2*:775, 1983).

CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), ß-endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science 213*:1394-1397, 1981). Briefly, CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science 224*:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol. 124*:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm. 110*:602-608, 1983), adrenals (Udelsman et al., *Nature 319*:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology 122*:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology 118*:1171-1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology 113*:657-662, 1983). The receptor for CRF has now been cloned from rat (Perrin et al., *Endo 133*(6):3058-3061, 1993), and human brain (Chen et al., *PNAS 90*(19):8967-8971, 1993; Vita et al., *FEBS 335*(1):1-5, 1993). This receptor is a 415 amino acid protein comprising seven membrane spanning domains. A comparison of identity

between rat and human sequences shows a high degree of homology (97%) at the amino acid level.

In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine, autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest. 90*:2555-2564, 1992; Sapolsky et al., *Science 238*:522-524, 1987; Tilders et al., *Regul. Peptides 5*:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature 297*:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res. 278*:332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology 110*:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology 110*:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences 30*:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol. 253*:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology 22*:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature 305*:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol. 255*:R744, 1988). Furthermore, clinical data suggests that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem. 25*:215-223, 1990). Accordingly, clinical data suggests that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

The first CRF receptor antagonists were peptides (*see, e.g.*, Rivier et al., U.S. Patent No. 4,605,642; Rivier et al., *Science 224*:889, 1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. Some published patent documents include US6313124, WO 01/23388, and WO 97/29109, all of which disclose pyrazolopyrimidine compounds as CRF antagonists. Published

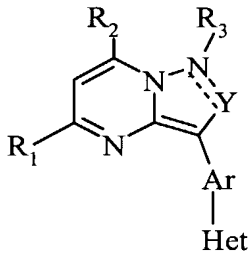
application WO 98/54093 described certain pyrazolopyrimidine compounds as tyrosine kinase inhibitors.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurological conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

In brief, this invention is generally directed to CRF receptor antagonists, and more specifically to CRF receptor antagonists having the following general structure (I):



(I)

and pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof, wherein R_1, R_2, R_3, Y, Ar, and Het are as defined below.

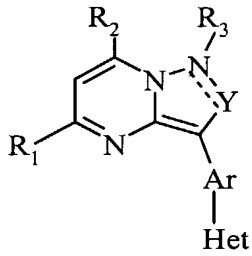
The CRF receptor antagonists of this invention may have utility over a wide range of therapeutic applications, and may be used to treat a variety of disorders or illnesses, including stress-related disorders. Such methods include administering a pharmaceutically effective amount of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition, to an animal in need thereof. Accordingly, in another embodiment, pharmaceutical compositions are disclosed containing one or more CRF receptor antagonists of this invention and a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to corticotropin-releasing factor (CRF) receptor antagonists.

In a first embodiment, the CRF receptor antagonists of this invention have the following structure (I):



(I)

or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof,

wherein:

"---" represents the second bond of an optional double bond;

R_1 is hydrogen, alkyl, substituted alkyl, heteroaryl, substituted heteroaryl, $-NH_2$, or halogen;

R_2 is alkyl, substituted alkyl, $-C(O)NR_7R_8$, aryl, substituted aryl, aryloxyalkyl, substituted aryloxyalkyl, heteroarylalkoxyalkyl, substituted heteroarylalkoxyalkyl, heterocyclealkyl, substituted heterocyclealkyl, arylalkyl, substituted arylalkyl, heteroaryl, or substituted heteroaryl, wherein said heteroaryl or substituted heteroaryl is connected to the pyrimidine ring via a carbon-carbon bond;

R_3 is null, hydrogen, or alkyl;

Y is $=(CR_4)-$ or $-(C=O)-$;

R_4 is hydrogen, alkyl, substituted alkyl, thioalkyl, alkylsulfinyl, or alkylsulfonyl;

Ar is phenyl, phenyl substituted with 1 or 2 R_5, pyridyl or pyridyl substituted with 1 or 2 R_5;

R_5 at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, halogen, alkylsulfonyl, or alkylsulfinyl;

Het is heteroaryl optionally substituted with 1 or 2 R_6;

R_6 at each occurrence is hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cyano, or halogen; and

R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, arylalkyl, substituted arylalkyl, heterocyclealkyl or substituted heterocyclealkyl; or

R_7 and R_8 taken together with the nitrogen to which they are attached form a heterocyclic ring or a substituted heterocyclic ring.

As used herein, the above terms have the following meaning:

"Alkyl" means a straight chain or branched, acyclic or cyclic, unsaturated or saturated hydrocarbon containing from 1 to 10 carbon atoms, while the term "lower alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -CH_2-cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cyclic alkyls, also referred to as "homocyclic rings," and include di- and poly-homocyclic rings such as decalin and adamantyl. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like.

"Alkylidenyl" represents a divalent alkyl from which two hydrogen atoms are taken from the same carbon atom, such as =CH_2, =$CHCH_3$, =$CHCH_2CH_3$, =$C(CH_3)CH_2CH_3$, and the like.

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with an aryl, such as benzyl (*i.e.,* -CH_2-phenyl), -CH_2-(1- or 2-naphthyl), -$(CH_2)_2$-phenyl, -$(CH_2)_3$-phenyl, -$CH(phenyl)_2$, and the like.

"Aryloxyalkyl" means an aryl attached through an oxygen bridge to an alkyl (*i.e.,* aryl-O-alkyl-) such as -methyl-O-phenyl, and such.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10-members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl, such as -CH_2-pyridinyl, -CH_2-pyrimidinyl, and the like.

"Heterocycle" (also referred to herein as a "heterocycle ring") means a 5- to 7-membered monocyclic, or 7- to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocyclic rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperizinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2-morpholinyl, and the like.

The term "substituted" as used herein refers to any group (*e.g.,* alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle or heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("-C(=O)-") two hydrogen atoms are replaced. "Substituents" within the context of this invention include halogen, hydroxy, cyano, nitro, amino, alkylamino, dialkylamino, alkyl, alkoxy, thioalkyl, haloalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aR_b$, -$NR_aC(=O)OR_b$ -$NR_aSO_2R_b$, -OR_a, -$C(=O)R_a$ -$C(=O)OR_a$, -$C(=O)NR_aR_b$, -$OC(=O)NR_aR_b$, -SH, -SR_a,

$-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$, $-S(=O)_2OR_a$, wherein R_a and R_b are the same or different and independently hydrogen, alkyl, haloalkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl.

"Halogen" means fluoro, chloro, bromo or iodo.

"Haloalkyl" means an alkyl having at least one hydrogen atom replaced with halogen, such as trifluoromethyl and the like. Haloalkyl is a specific embodiment of substituted alkyl, wherein alkyl is substituted with one or more halogen atoms.

"Alkoxy" means an alkyl attached through an oxygen bridge (*i.e.,* -O-alkyl) such as –O-methyl, -O-ethyl, and the like.

"Thioalkyl" means an alkyl attached through a sulfur bridge (*i.e.,* -S-alkyl) such as –S-methyl, -S-ethyl, and the like.

"Alkylamino" and "dialkylamino" mean one or two alkyl moieties attached through a nitrogen bridge (*i.e.,* -NHalkyl or –N(alkyl)(alkyl)) such as methylamino, ethylamino, dimethylamino, diethylamino, and the like.

"Hydroxyalkyl" means an alkyl substituted with at least one hydroxy group.

"Mono- or di(cycloalkyl)methyl" represents a methyl group substituted with one or two cycloalkyl groups, such as cyclopropylmethyl, dicyclopropylmethyl, and the like.

"Alkylcarbonylalkyl" represents an alkyl substituted with a -C(=O)alkyl group.

"Alkylcarbonyloxyalkyl" represents an alkyl substituted with a -C(=O)Oalkyl group or a -OC(=O)alkyl group.

"Alkoxyalkyl" represents an alkyl substituted with a -O-alkyl group.

"Alkylthioalkyl" represents a alkyl substituted with a -S-alkyl group.

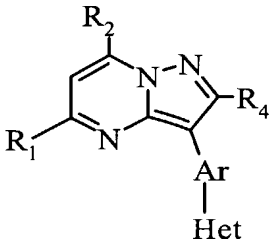
"Mono- or di(alkyl)amino represents an amino substituted with one alkyl or with two alkyls, respectively.

"Mono- or di(alkyl)aminoalkyl" represents an alkyl substituted with a mono- or di(alkyl)amino.

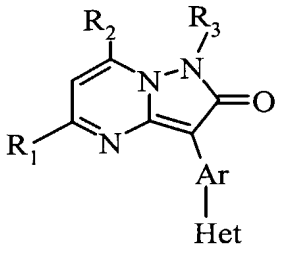
"Alkylsulfonyl or alkylsulfinyl" represents an alkyl substituted with a ($-S(=O)_2-$) or (-S(=O)-) functionality, respectively.

Embodiments of this invention presented herein are for purposes of example and not for purposes of limitation. In a first embodiment of the invention, R_3 is

null and Y is =(CR_4)- in the following structure (II), and in a further embodiment Y is -(C=O)- in the following structure (III).

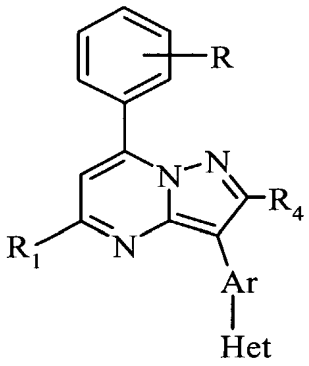


(II)



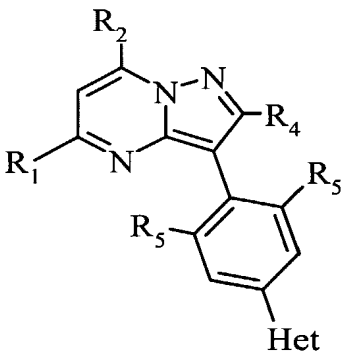
(III)

Further embodiments of this invention have structure (IV) when R_2 is phenyl, R is an optional substituent of said phenyl, and Y is =(CR_4)-.

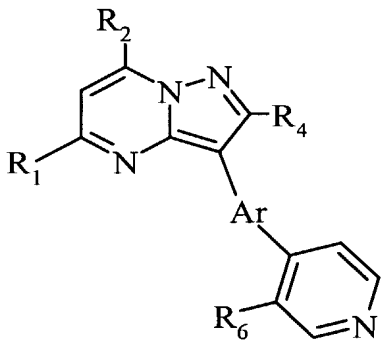


(IV)

In further embodiments of this invention wherein Y is =(CR_4)-, Ar is phenyl substituted with 2 R_5 in structure (V) and Het is pyridyl substituted with 1 R_6 in structure (IV).



(V)



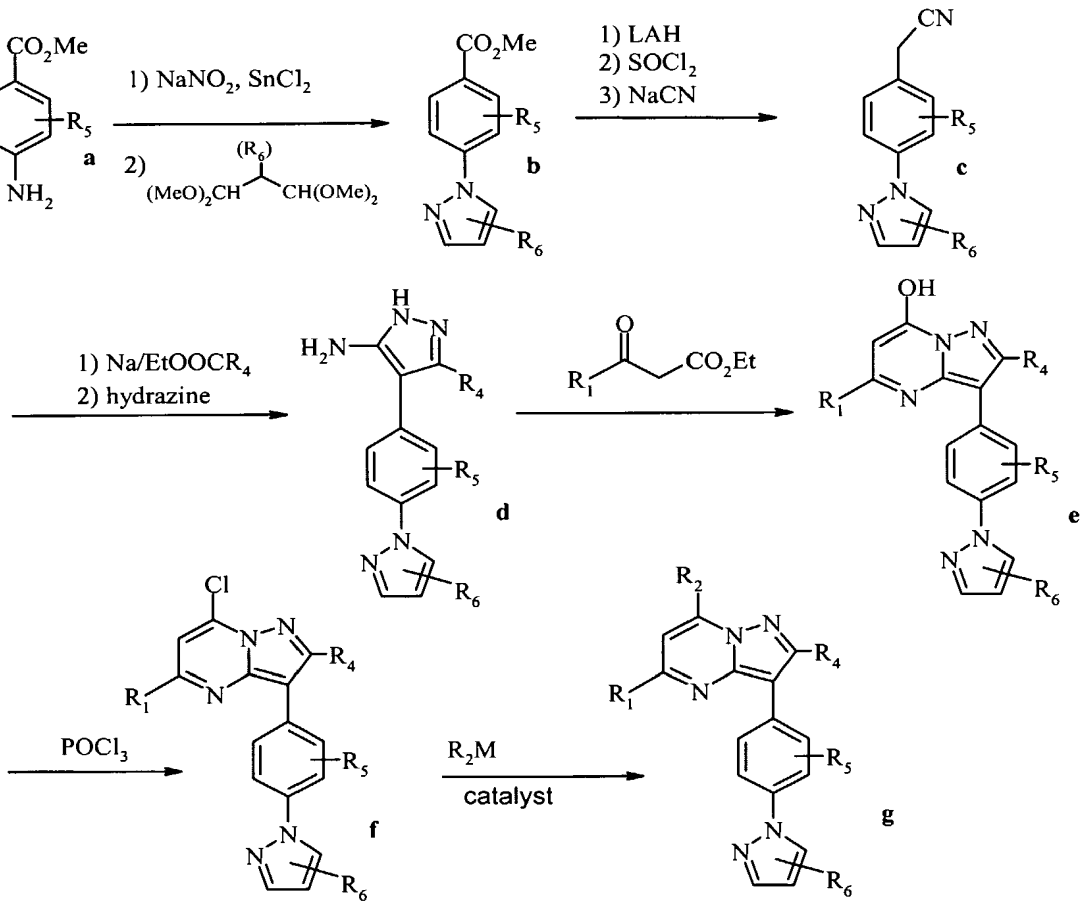
(VI)

The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form

of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all pharmaceutically acceptable salt forms.

In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples. Examples of synthetic procedures which may be used to prepare compounds according to the invention are illustrated in Reaction Schemes 1-3.

Reaction Scheme 1

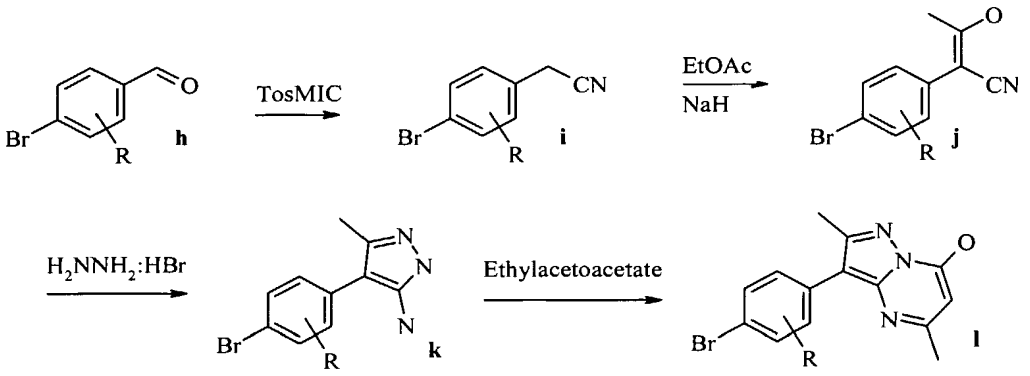


The amino functionality of 4-aminobenzoate **a** may be condensed with an, optionally, substituted malonaldehyde to give the corresponding 4-pyrazol-1-yl benzoate **b**. After reaction with LAH, $SOCl_2$, and NaCN to give conversion to the pyrazolophenylacetonitrile compound **c**, reaction with Na/ethyl carboxylic acid ester and hydrazine yields the bis-pyrazole **d**. Reaction with the appropriately substituted β-keto ester gives pyrazolopyrimidine **e** which reacts with $POCl_3$ to give the chloride **f**. Reaction of the chloride **f** with an appropriate organometallic reagent R_2M in the presence of a suitable catalyst or promoter gives compound **g**. Examples of suitable organometallic reagents and suitable catalysts/promoters include:

1. (substituted) alkyl grignard reagents R_2MgX ($Fe(acac)_3$ promoter);
2. aryl, heteroaryl, or alkenyl boronic acids or esters ($Pd(PhP)_4$ catalyst); and
3. aryl or heteroaryl zinc reagents ($Pd(PhP)_4$ catalyst).

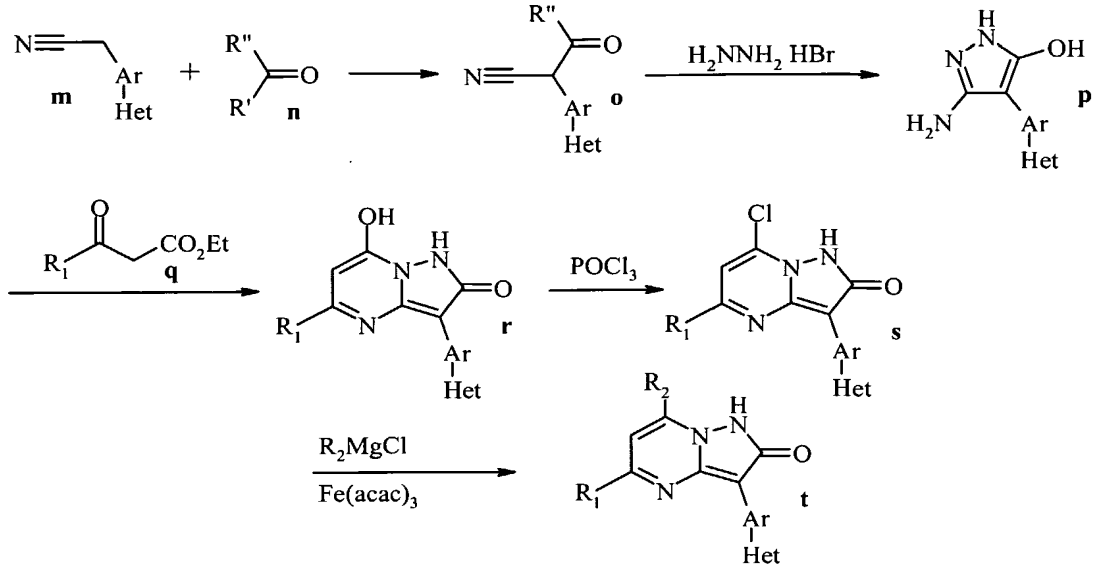
The R_2 groups thus installed may be further manipulated or reacted, using standard methods known to those skilled in the art (for example oxidation/reduction, hydrolysis, and the like), to provide further examples of the invention.

Reaction Scheme 2



Multiple synthetic routes to the pyrazolopyrimidine core of the invention are available. In Reaction Scheme 2, the optionally substituted halobenzaldehyde **h** reacts with tosylmethyl isocyanide (TosMIC) to form the phenylacetonitrile **i**. Reaction of **i** with NaH and EtOAc gives the 3-hydroxy but-2-enenitrile **j** which undergoes ring closure in reaction with hydrazine HBr to give the 3-amino 2-phenyl pyrazole **k**. Addition of the β-keto ester gives the pyrazolo[1,5-a]pyrimidin-7-ol **l**. Substitution of the oxygen as in Reaction Scheme 1 and substitution of the distal bromine with Het gives compounds according to the invention.

Reaction Scheme 3



Reaction of substituted acetonitrile **m** with ketone **n**, where R' is a good leaving group such as alkoxy, cyano, or halo and where R" is a group such as hydroxy or alkoxy gives cyanoketone **o** which reacts with hydrazine to give substituted pyrazole **p**. Reaction of **p** with β-keto ester **q** gives pyrazolopyrimidine **r**. Reaction with $POCl_3$ gives the chloride **s**, and substitution of chloride by R_2 gives compound **t**.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention may be capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse 1*:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (*e.g.*, [^{125}I]tyrosine-CFR) to its receptor (*e.g.*, receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC_{50} as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation:

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)).

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM. In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1μM, and more preferably less than 0.25 μM (*i.e.,* 250 nM). As set forth in greater detail below, the K_i values may be assayed by the methods set forth in Example 27.

CRF receptor antagonists of the present invention may demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurological disorders or illnesses. More specifically, CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, CRF receptor antagonists of the present invention may be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression

associated with various diseases states, as well as stroke. Other uses of CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), pain, Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present

invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist in alternative crystalline, amorphous or polymorphic forms as polymorphs, all of which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurological disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention may be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

In another embodiment, the present invention permits the diagnostic visualization of specific sites within the body by the use of radioactive or non-radioactive pharmaceutical agents. Use of a compound of the present invention may provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. Radioactive pharmaceuticals are employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and single photon emission computerized tomography (SPECT.) For such applications, radioisotopes are incorporated of such elements as iodine (I) including ^{123}I (PET), ^{125}I (SPECT), and ^{131}I, technetium (Tc) including ^{99}Tc (PET), phosphorus (P) including ^{31}P and ^{32}P, chromium (Cr) including ^{51}Cr, carbon (C) including ^{11}C, fluorine (F) including ^{18}F, thallium (Tl) including ^{201}Tl, and like emitters of positron and ionizing radiation. Non-radioactive pharmaceuticals are employed in magnetic resonance imaging (MRI), fluoroscopy, and ultrasound. For such applications, isotopes are incorporated of such elements as gadolinium (Gd) including ^{153}Gd, iron (Fe), barium (Ba), manganese (Mn), and thallium (Tl). Such entities are

also useful for identifying the presence of particular target sites in a mixture and for labeling molecules in a mixture.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, pain, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

The CRF receptor antagonists of this invention may be prepared by the methods disclosed in Examples 1 to 26. Example 27 presents a method for determining the receptor binding affinity, and Example 28 discloses an assay for screening compounds of this invention for CRF-stimulated adenylate cyclase activity.

Analytical HPLC-MS Method 1

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: YMC ODS AQ, S-5, 5µ, 2.0 x50 mm cartridge;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 2

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: Phenomenex Synergi-Max RP, 2.0 x 50 mm column;

HPLC gradient: 1.0 mL/minute, from 5 % acetonitrile in water to 95 % acetonitrile in water in 13.5 minutes, maintaining 95 % for 2 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 3

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: XTerra MS, C_{18}, 5µ, 3.0 x 250 mm column;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 46 minutes, jump to 99% acetonitrile and maintain 99 % acetonitrile for 8.04 minutes. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 4

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI) and Berger FCM 1200 CO_2 pump module;

HPLC column: Berger Pyridine, PYR 60A, 6µ, 4.6 x 150 mm column;

HPLC gradient: 4.0 mL/minute, 120 bar; from 10 % methanol in supercritical CO_2 to 60% methanol in supercritical CO_2 in 1.67 minutes, maintaining 60 % for 1 minute. Methanol has 1.5% water. Backpressure regulated at 140 bar.

Preparative HPLC-MS

Platform: Shimadzu HPLC equipped with a Gilson 215 auto-sampler/fraction collector, UV detector and a PE Sciez API150EX mass detector;

HPLC column: BHK ODS-O/B, 5 µ, 30x75 mm

HPLC gradient: 35 mL/minute, 10% acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes, with 0.025% TFA.

Abbreviations:

AA: Acetyl acetate

LAH: Lithium aluminum hydride

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

EAA: Ethyl acetoacetate

LC-MS: liquid chromatography-mass spectroscopy

$NaBH(OAc)_3$: Sodium Triacetoxyborohydride

Pd-C: Palladium (10 %) on Carbon

TFA: Trifluoroacetic acid

Tosmic: Tosylmethyl isocyanide

acac: acetylacetonate

EDCI: N-ethyl-N'-(dimethylaminopropyl)carbodiimide hydrochloride

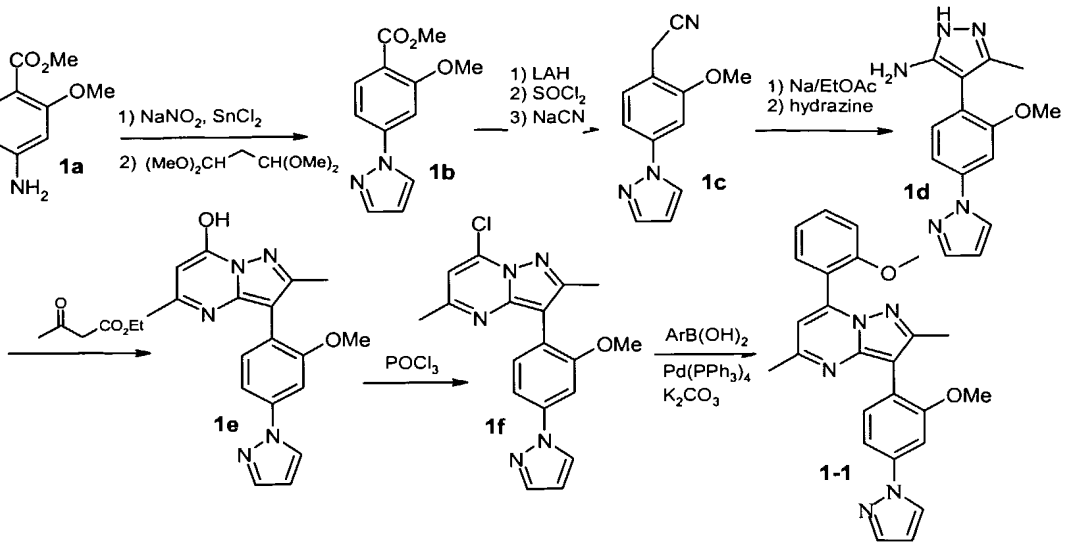
THF: tetrahydrofuran

TEA: triethylamine

t_R: Retention time

EXAMPLE 1

7-(2-METHOXY-PHENYL)-3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



Step 1A:

To a cooled suspension of methyl 4-amino-2-methoxybenzoate (6.82 g, 37.7 mmol) in 6N HCl (aqueous) was added a solution of sodium nitrite (2.60 g, 37.7 mmol) dropwise. After stirring at 0 °C for 20 min, stannous chloride dihydrate (24.7 g, 109.3 mmol) was added portionwise. The resulting suspension was stirred at 0 °C for 1.5 hr prior to filtration. The collected solid was suspended in EtOH to which malonaldehyde bis(dimethyl acetal) (7.5 mL, 45.7 mmol) was added, and this reaction mixture was subjected to reflux overnight. After evaporation of EtOH, the residue was extracted between EtOAc and water, and the organic phase was dried and evaporated to dryness. The residue was passed through a silica gel plug (25% EtOAc/hexane) to yield Cmpd **1b** (7.43 g) as a mixture of the methyl and ethyl benzoate.

Step 1B:

To a solution of **1b** (10.6 g) in dry diethyl ether (200 mL) was added LAH powder (1.74 g) slowly at 0 °C. After stirring for 45 min at 0 °C the reaction mixture was decanted onto ice-water, and the aqueous phase was acidified to pH 4.0. After isolation, the alcohol (8.8 g) was refluxed with thionyl chloride (10 mL) in DCM for 2.5 hr, decanted onto ice-water, and extracted with DCM. The crude benzyl chloride (8.26 g) was heated with NaCN (3.65 g, 74.4 mmol) in DMSO (100 mL) at 80 °C for 45 min. After removal of DMSO, Cmpd **1c** (5.98 g) obtained after column chromatography with 30% EtOAc/hexane.

Step 1C:

To a solution of **1c** (5.98 g, 28.1 mmol) in EtOAc (150 mL) was added metallic sodium (1.0 g, 43.5 mmol) portionwise, and the mixture was refluxed overnight. The resulting suspension was decanted onto ice-water and acidified to pH 4.0. The organic phase was dried and evaporated to dryness. The resulting compound (9.5 g) was mixed with hydrazine monohydrobromide (15.3 g, 135.4 mmol,) and refluxed in EtOH/H_2O (6:1) for 5 hr. After evaporation of EtOH and extraction with EtOAc, the organic phase was dried and evaporated to dryness to yield Cmpd **1d** (7.5 g.)

Step 1D:

A mixture of **1d** (7.5 g, 27.9 mmol) was refluxed with ethyl acetoacetate (5.0 mL) in AcOH (100 mL) for 3 hr. After evaporation of AcOH and precipitation in diethyl ether, Cmpd **1e** (10.4 g) obtained after filtration.

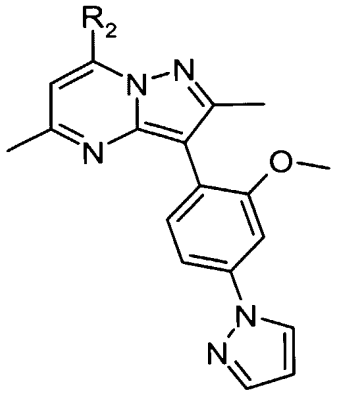
Step 1E:

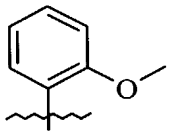
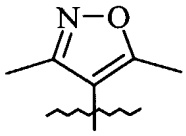
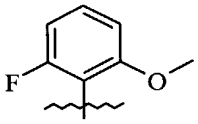
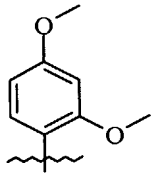
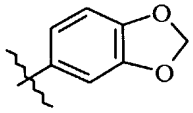
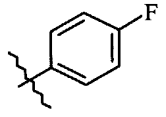
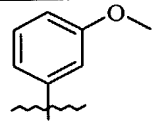
To a suspension of **1e** (2.1 g, 6.3 mmol) in acetonitrile was added $POCl_3$ (2.2 mL, 24.1 mmol,) and this mixture was refluxed for 5 hr, decanted to ice-water, and extracted with EtOAc to yield Cmpd **1f** (1.88 g) after chromatographic purification.

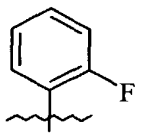
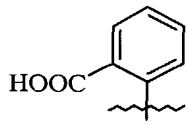
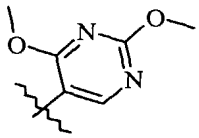
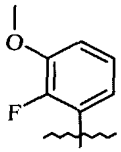
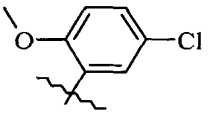
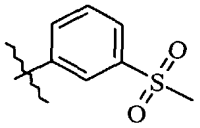
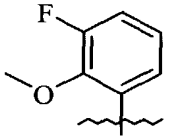
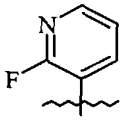
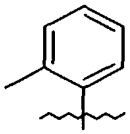
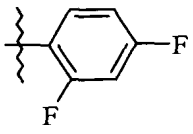
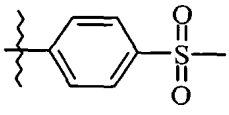
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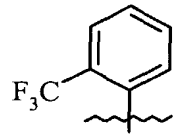
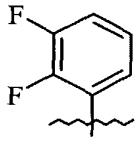
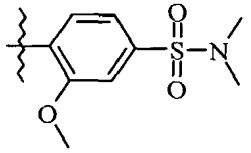
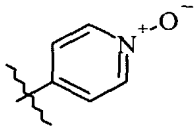
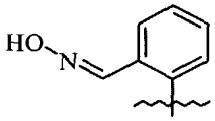
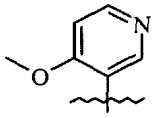
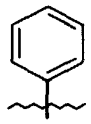
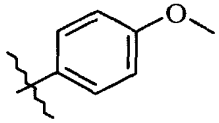
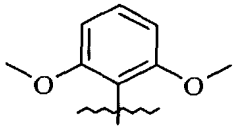
A mixture of Cmpd **1f** (1.0 mmol), 2-methoxyphenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) was heated in 1,4-dioxane/H_2O (2:1) at 110 °C overnight. After evaporation of solvent, the mixture was extracted between $CHCl_3$/H_2O, and the organic phase was dried and evaporated to dryness. Cmpd **1-1** (402 mg) was obtained after column chromatography. Depending on the

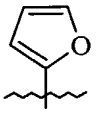
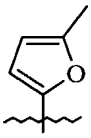
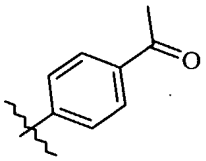
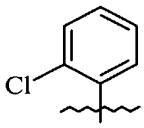
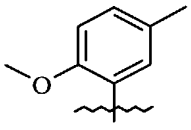
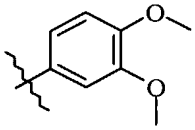
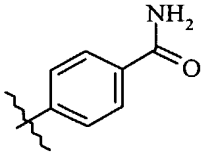
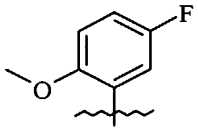
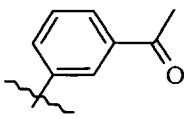
aryl functionality in the arylboronic acid reagent, the compounds listed in the following table were synthesized and purified by preparative LC-MS:

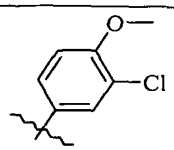
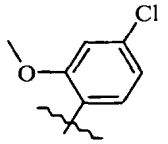
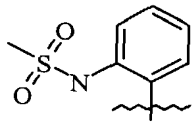
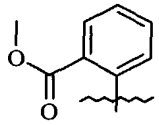
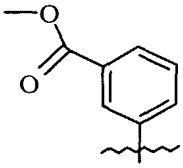
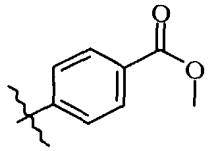
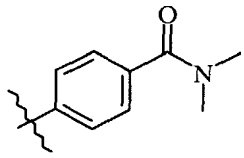
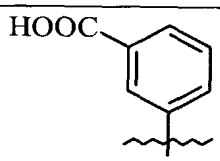
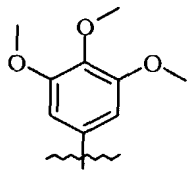
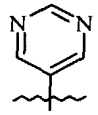


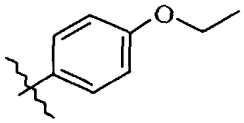
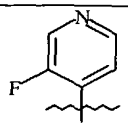
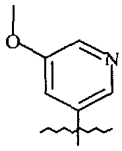
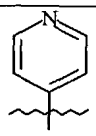
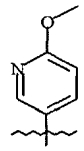
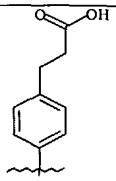
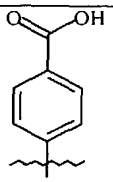
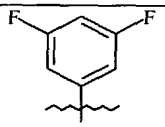
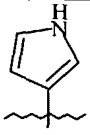
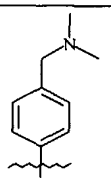
Cmpd	R_2	MW	MS	t_R	HPLC Method
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1-2		414.47	414	1.586	4
1-3		443.48	443	1.335	4
1-4		455.52	455	1.32	4
1-5		439.47	439	1.353	4
1-6		413.45	413	1.25	4
1-7		425.49	425	1.317	4

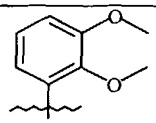
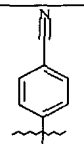
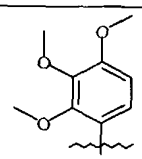
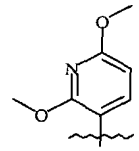
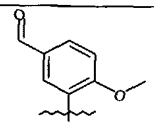
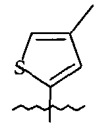
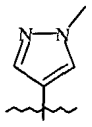
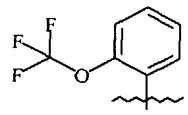
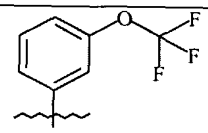
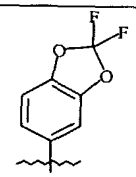
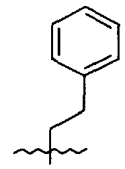
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-8		413.45	413	1.236	4
1-9		439.47	439	5.625	2
1-10		457.49	457	7.09	2
1-11		443.48	443	1.226	4
1-12		459.94	459	1.188	4
1-13		473.56	473	1.446	4
1-14		443.48	443	1.120	4
1-15		414.44	414	1.242	4
1-16		409.49	409	1.088	4
1-17		431.44	431	1.071	4
1-18		473.56	473	1.514	4

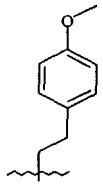
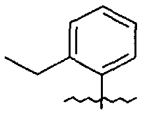
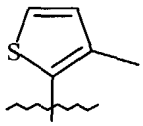
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1-20		431.44	431	1.165	4
1-21		502.60	502	1.469	4
1-22		412.45	412	1.506	4
1-23		438.49	438	6.463	2
1-24		426.48	426	4.405	2
1-25		395.46	396	8.240	2
1-26		425.49	425.9	8.260	2
1-27		455.52	456	7.550	2
1-28		401.49	401.9	8.490	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-29		401.49	401.9	8.530	2
1-30		385.42	385.9	8.410	2
1-31		399.45	335.9	4.700	2
1-32		385.42	385.9	8.300	2
1-33		437.50	437	7.861	2
1-34		429.912	429	8.229	2
1-35		439.512	439	8.320	2
1-36		455.52	455	7.718	2
1-37		438.49	438	6.153	2
1-38		443.48	443	1.218	4
1-39		437.50	437	7.807	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-40		459.94	459	8.956	2
1-41		459.94	459	8.598	2
1-42		488.57	488	7.216	2
1-43		453.50	454	7.601	2
1-44		453.50	454	8.310	2
1-45		453.50	454	8.380	2
1-46		466.54	467	6.690	2
1-47		439.47	440	7.010	2
1-48		485.54	486	8.000	2
1-49		397.44	398	6.270	2

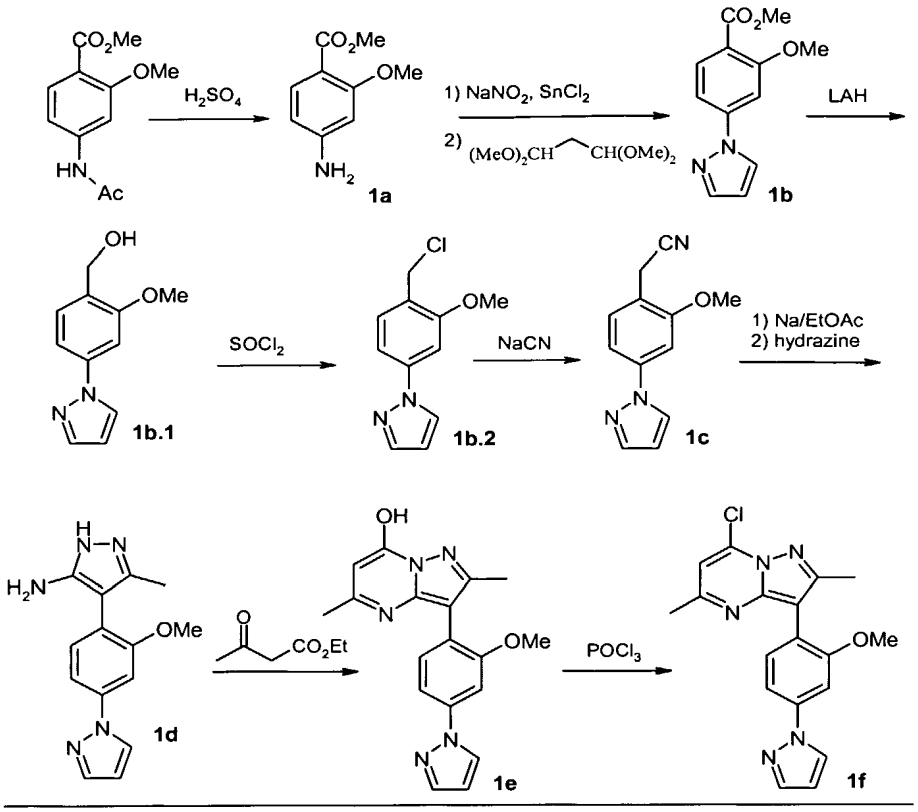
Cmpd	R_2	MW	MS	t_R	HPLC Method
1-50		439.52	439	8.288	2
1-51		414.44	414	5.640	2
1-52		426.48	426	5.910	2
1-53		396.45	396	4.920	2
1-54		426.48	426	6.630	2
1-55		467.53	468	6.970	2
1-56		439.47	440	6.710	2
1-57		431.44	432	8.660	2
1-58[1]		384.44	385	5.390	2
1-59		452.56	453	4.590	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-60		455.52	455	6.170	2
1-61		420.47	420	1.410	4
1-62		485.54	486	7.540	2
1-63		456.50	456	8.120	2
1-64		453.50	454.3	5.710	2
1-65		415.52	415	6.770	2
1-66		399.46	399	6.430	2
1-67		479.46	479	6.740	2
1-68		479.46	479	7.260	2
1-69		475.45	475	6.970	2
1-70		423.52	423	6.370	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
1-71		453.54	453	6.280	2
1-72		423.52	423	8.420	2
1-73		415.52	415	8.080	2

EXAMPLE 1A

ALTERNATE SYNTHESIS OF INTERMEDIATE 1F



Step 1A-A:

To a 3-neck flask equipped with a mechanical stirrer was charged 250 g (1.12 mol) of 2-methoxy-4-acetylaminobenzoic acid methyl ester followed by 1L of methanol. Agitation was started and 94 mL (3.36 mmol, 3 eq.) of concentrated sulfuric acid was slowly added creating a slight reflux. The mixture was stirred for 24 hr. The mixture was concentrated *in vacuo* affording a thick slurry. The slurry was filtered using a Buchner funnel and washed with 300 mL of cold methanol. The filter cake was collected and dried in vacuo at 45 °C for 24 hr affording 302 g of **1a** as a hemi-sulfate salt in a 96% yield.

Step 1A-B:

In a 2L three-neck Morton flask equipped with a mechanical stirrer and thermocouple was charged 200 g (716 mmol) of methyl 4-amino-2-methoxybenzoate

1a. The solid was slurried with 700 mL of 6N hydrochloric acid and chilled in an ice-bath. To the mixture was charged dropwise 54.3 g (788 mmol, 1.1 eq.) of sodium nitrite in 100 mL of water maintaining a temperature of <15 °C during the addition. The mixture was stirred an additional 1.5 hr affording a light yellow, homogeneous solution. To the mixture was carefully added 272 g (1432 mmol, 2 eq.) of anhydrous stannous chloride. The temperature during the addition was kept <10 °C. The mixture was stirred at 0 °C for 1 hr, and then stored at 5 °C for 16 hr. The precipitate was collected by filtration through a Buchner funnel and the filter cake air dried for 2 hr. The filter cake was transferred to a 2 L round bottom flask equipped with a magnetic stir bar and diluted with 600 mL of ethanol. To the slurry was charged 142 mL (859 mmol, 1.2 eq.) of malonaldehyde bis(dimethyl acetal) and the mixture refluxed for 6 hr. After evaporation of ethanol, the residue was diluted with ethyl acetate and neutralized with sodium hydroxide. The organic phase was separated, dried and concentrated in vacuo. The crude product was passed through a silica gel plug eluting with 25% ethyl acetate in hexane affording 96 g of Cmpd **1b** in a 58% yield as a mixture of the methyl and ethyl esters.

Step 1A-C:

To a 1L round bottom flask containing 500 mL dry THF was added LAH (14.5 g, 380 mmol, 0.95 eq), and the mixture was cooled to 0 °C. To this mixture was added dropwise a solution of **1b** (96 g, 400 mmol, 1.0 eq) in 300 mL THF. The temperature was maintained below 15 °C during the addition. After the addition was complete, the mixture was stirred for 1 hr, then the reaction mix was carefully quenched with water (14.5 mL), 10% aq. sodium hydroxide (14.5 mL), and water (43.5 mL). The resulting mixture was filtered through a pad of Celite® and concentrated to provide **1b.1** as a slightly yellow oil (63.9 g, 75.7%), which was used without further purification.

Step 1A-D:

Thionyl chloride (95 mL, 1.30 mol, 3.1 eq) was added dropwise over 1 hr to a solution of **1b.1** (85.0 g, 0.42 mol) in 400 mL DCM, keeping the rate of addition such that a gentle reflux was maintained. A precipitate formed, which re-dissolved upon completion of the addition. The resulting dark solution was refluxed for 4 hr. The cooled reaction mixture was poured onto 500 g of ice, and the resulting mixture was extracted with 2 x 700 mL of DCM. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and

concentrated to provide **1b.2** (76.5 g) as a brown solid, which was used without further purification.

Step 1A-E:

A solution of **1b.2** (76 g, 340 mmol, 1.0 eq.) in DMF (100 mL) was added dropwise over 20 min. to a mixture of sodium cyanide (24.5 g, 500 mmol, 1.5 eq) and DMF (300 mL) heated to 100 °C. The mixture was heated at 100 °C for 4 hr, then the cooled mixture was filtered through Celite®. The filtrate was concentrated, then the residue was taken up in 300 mL DCM and washed with saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to provide a dark brown solid residue. This residue was slurried in ethanol (100 mL), then the solid was collected by filtration and washed with cold ethanol and ether, providing **1c** (48.0 g) as an off-white solid. The mother liquid was concentrated and purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide an additional 15.4 g of **1c** as a white solid. Combined yield 63.4 g.

Step 1A-F:

To a solution of **1c** (63.4 g, 0.30 mol, 1 eq) in ethyl acetate (800 mL) was added metallic sodium (10.3 g, 0.45 mmol, 1.5 eq) portionwise, and the mixture was refluxed for 16 hr The cooled suspension was poured onto 500 g ice, acidified to pH 5, then extracted with 2 x 300 mL ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated to a crude yellow oil (86.5 g).

The crude yellow oil (86.5 g) was dissolved in ethanol (480 mL) and water (80 mL), then hydrazine monohydrobromide (100 g, 0.88 mol, 3 eq) was added and the mixture was heated at 85 °C for 16 hr. The solvents were evaporated, brine (200 mL) was added, and the mixture was extracted with 2 x 300 mL ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to provide **1d** (68 g) as a crude brown foam, which was used without further purification.

Step 1A-G:

A mixture of **1d** (68 g, 250 mmol, 1.0 eq), ethyl acetoacetate (100 mL), acetic acid (150 mL), and ethanol (150 mL) was refluxed for 24 hr. The cooled mixture was concentrated to provide a solid residue, which was then deposited onto a fritted glass filter and washed with ether, providing **1e** (52.0 g, 51.2%) as an off-white solid.

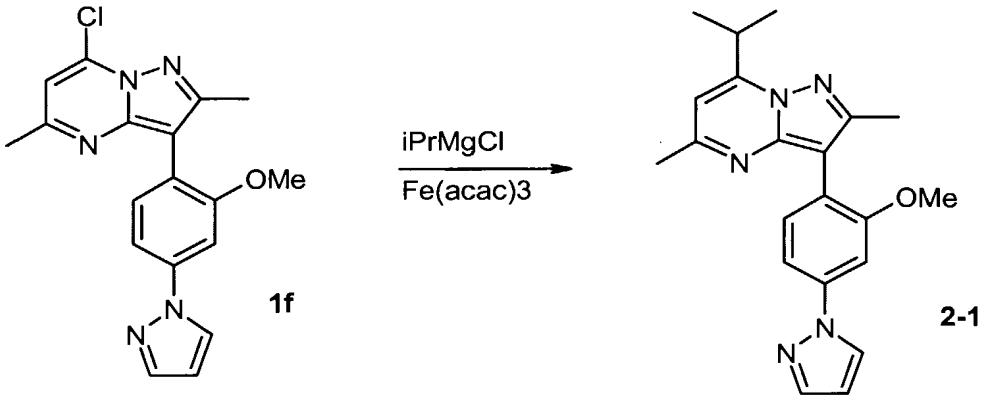
The mother liquor was concentrated, then chromatographed on silica gel using 10% methanol in DCM as eluent. The solid product thus obtained was washed with ether to provide an additional 17.0 g of **1e** as an off-white solid (combined yield 69 g).

Step 1A-H:

To a suspension of **1e** (41.2 g, 123 mmol) in acetonitrile (200 mL) was added $POCl_3$ (45.0 mL, 493 mmol,) and this mixture was refluxed for 16 hr. The cooled reaction mixture was poured onto ice-water, and the resulting mixture was extracted with chloroform. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 3:1 hexanes/ethyl acetate, to yield **1f** (29.0 g) as a tan solid.

EXAMPLE 2

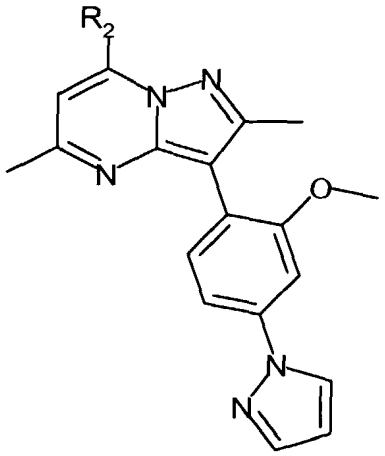
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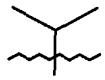
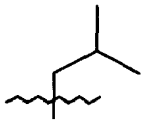
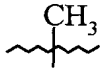
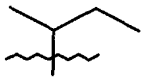
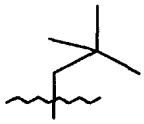
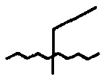
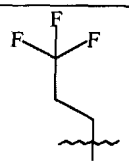
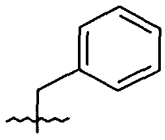


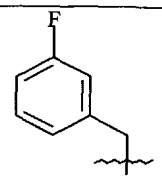
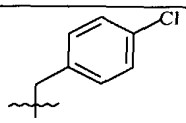
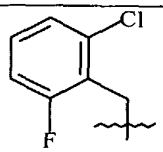
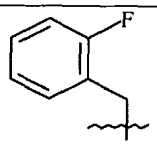
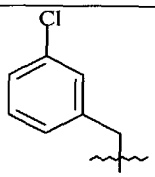
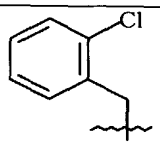
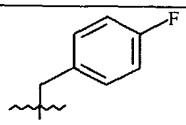
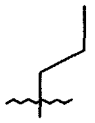
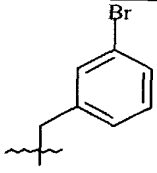
Step 2A:

To a solution of Cmpd **1f** (1.41 g, 4.0 mmol) and $Fe(acac)_3$ (424 mg, 1.2 mmol) in THF/NMP (v/v = 8:1) was added iPrMgCl (2.0 M in THF, 4.0 mL) slowly at room temperature. The reaction mixture was stirred for 1.5 hr before quenched with 1N HCl (aq.). After extraction with EtOAc, the crude product was purified by column chromatography (25% EtOAc/Hexane) to yield Cmpd **2-1** (628 mg.)

Depending on the alkyl functionality in the alkyl magnesium halide, the compounds listed in the following table were synthesized:

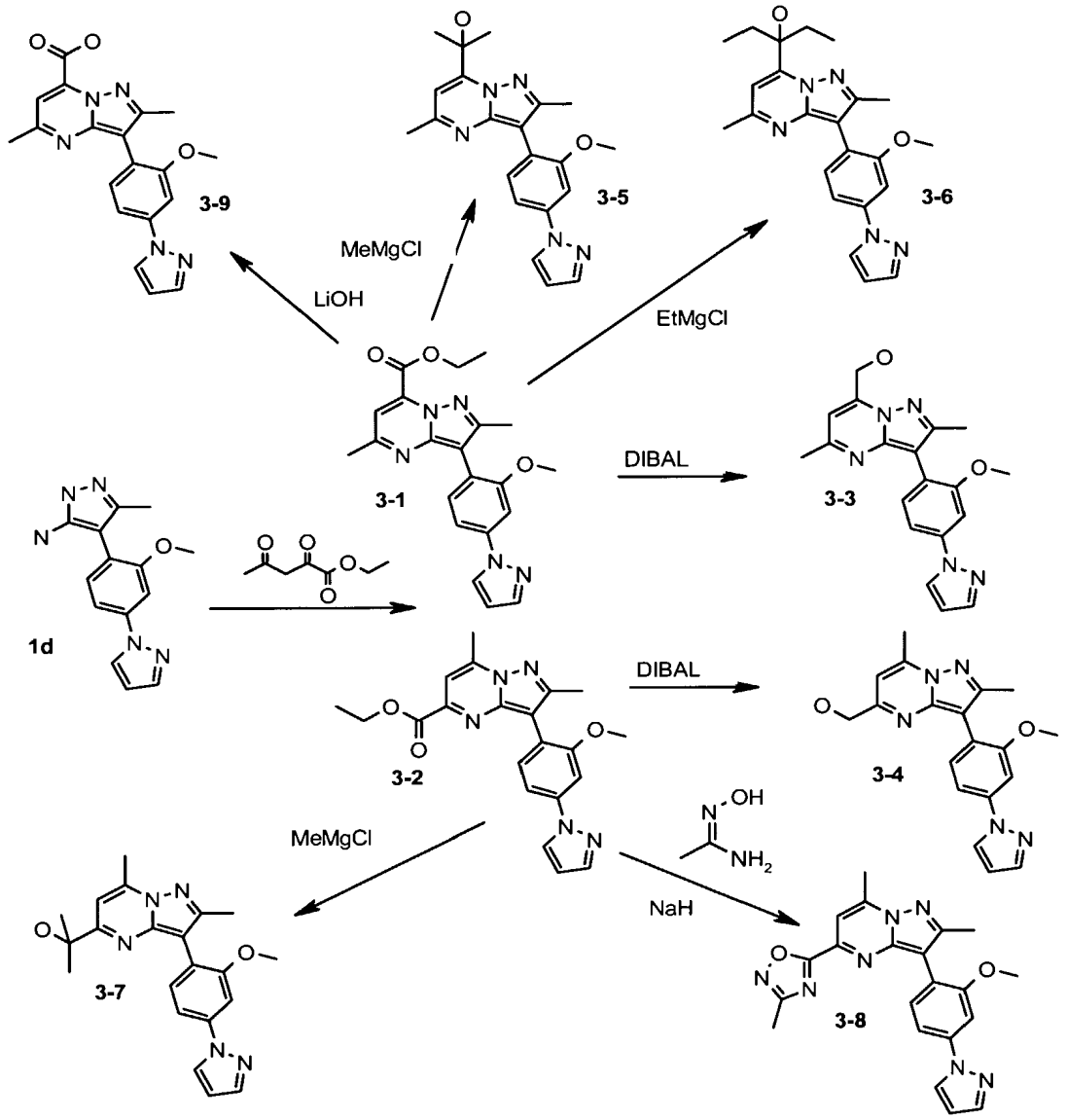


Cmpd	R_2	MW	MS	t_R	HPLC Method
2-1		361.447	361	1.286	4
2-2		375.474	375	1.499	4
2-3		333.393	333	1.542	4
2-4		375.474	375	1.278	4
2-5		389.5	390.2	8.490	2
2-6		347.42	348	6.514	2
2-7		415.417	415	7.880	2
2-8		409.491	409	6.280	2

Cmpd	R_2	MW	MS	t_R	HPLC Method
2-9		427.481	428	8.240	2
2-10		443.936	444	8.790	2
2-11		461.926	462	8.740	2
2-12		427.481	428	8.240	2
2-13		443.936	444	8.750	2
2-14		443.936	444	8.660	2
2-15		427.481	428	8.240	2
2-16		361.447	361	2.700	1
2-17		488.387	488	8.920	2

EXAMPLE 3

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID ETHYL ESTER



Step 3A:

To 20 mL EtOH were added Cmpd **1d** (1.0 g, Example 1, Step 1C) and ethyl-2,4-dioxovalerate (0.82 g) followed by 0.5 mL acetic acid. The reaction mixture was heated at 80 °C for 12 hr. Concentration and purification by silica gel column

chromatography yielded Cmpd **3-1** (0.66 g, 46.1% yield) and the inverted addition Cmpd **3-2** (0.47 g, 32.2% yield.)

Step 3B:

To Cmpd **3-1** (30 mg) dissolved in THF (1.5 mL) was added DIBAL (150 uL of 2 M DIBAL in hexane.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water (0.4 mL.) After purification via LC-MS, Cmpd **3-3** (3.3 mg) obtained. Following the same procedure, the reduction of Cmpd **3-2** afforded Cmpd **3-4** (2.6 mg) after purification.

Step 3C:

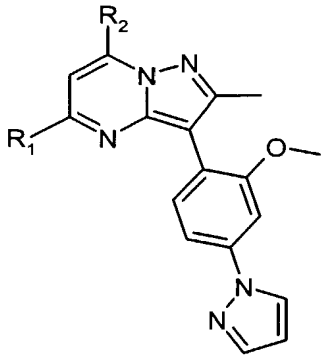
To 1.5 mL THF was added Cmpd **3-1** (30 mg) followed by CH_3MgBr (150 uL of 2 M CH_3MgBr in THF.) The reaction mixture was stirred at room temperature for 2 hr and quenched with water. The resulting material was purified by LC-MS to yield Cmpd **3-5** (3.8 mg.) Following this procedure with Cmpd **3-1** and CH_3CH_2MgBr yielded Cmpd **3-6** (4.1 mg.) after purification. Following the same reaction procedure employing Cmpd **3-2** as the starting reagent and CH_3MgBr as nucleophile afforded Cmpd **3-7** (4.0 mg) after purification.

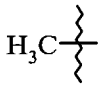
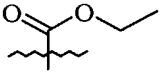
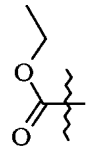
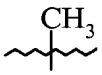
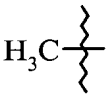
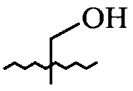
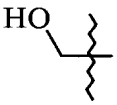
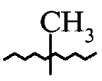
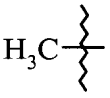
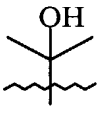
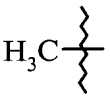
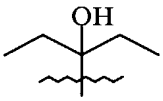
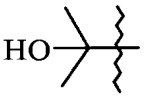
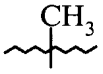
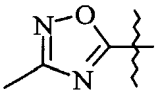
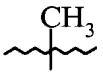
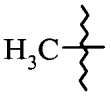
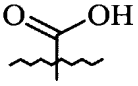
Step 3D:

To THF (1.5 mL) was added acetamidoxime (20 mg) and NaH (10 mg) with stirring at room temperature for 30 min. Cmpd **3-2** (40 mg) was added, and the mixture was heated at 90 °C for 2 hr in a sealed tube. After purification via LC-MS, Cmpd **3-8** obtained (5.5 mg.)

Step 3E:

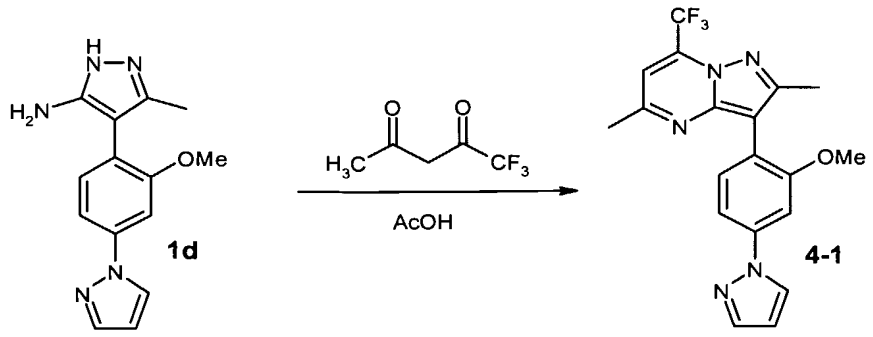
To Cmpd **3-1** (200 mg) in dioxane:water (9:1) was added LiOH (30 mg.) The reaction proceeded with stirring for 6 hr at room temperature followed by quenching to pH 4 (HCl, 4 N) and extraction between H_2O (20 mL) and EtOAc (20 mL.) The organic phase was dried over Na_2SO_4 and concentrated. The resulting concentrate was purified by silica gel column chromatography (50:50 EtOAc/hexane) to yield Cmpd **3-9** (180 mg.) Compounds presented in Example 3 are tabulated in the following table:



Cmpd	R_1	R_2	MW	MS	t_R	HPLC Method
3-1			391.429	392	2.681	1
3-2			391.429	392	6.850	2
3-3			349.392	350	5.060	2
3-4			349.392	350	5.030	2
3-5			377.446	378	6.880	2
3-6			405.499	406	7.980	2
3-7			377.446	378	1.264	4
3-8			401.428	402	6.990	2
3-9			363.375	364	5.740	2

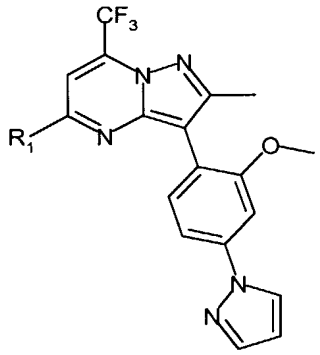
EXAMPLE 4

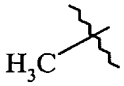
3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-TRIFLUOROMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE



Step 4A:

A mixture of Cmpd **1d** (40 mg, Example 1, Step 1C) and 1,1,1-trifluoropentane-2,4-dione (excess) was heated in AcOH at 150 °C for 15 min with microwave to afford after purification via LC-MS Cmpd **4-1** (29 mg.) Depending on the trifluorodione, the compounds in the following table were synthesized:

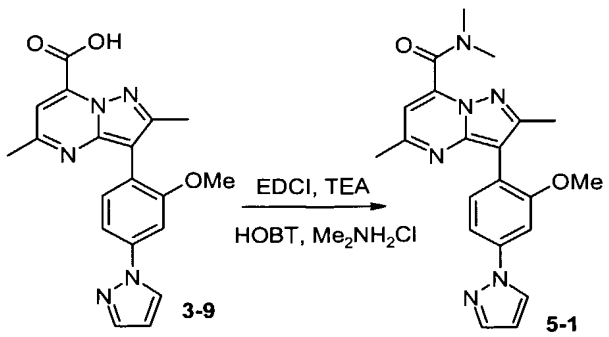


Cmpd	R_1	MW	MS	t_R*
4-1		387.363	387	6.215
4-2		415.417	415	6.928

* All HPLC determinations employed Analytical Method 2.

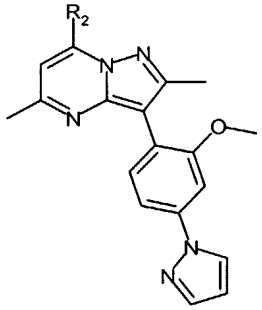
EXAMPLE 5

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDINE-7-CARBOXYLIC ACID DIMETHYLAMIDE



Step 5A:

To a solution of Cmpd **3-9** (50 mg, 0.14 mmol, 1 eq) in DCM (1 mL) was added HOBT (57 mg, 0.42 mmol, 3 eq), TEA (0.12 mL, 0.84 mmol, 6 eq), dimethylamine hydrochloride (34 mg, 0.42 mmol, 3 eq) and EDCI (79 mg, 0.42 mmol, 3 eq). The mixture was stirred at room temperature for 16 hr, then the solvent was evaporated, and the crude reaction mixture was purified by preparative HPLC/MS, providing Cmpd **5-1** (10 mg) as a TFA salt. Depending on the amine employed in the amidation step above, the compounds in the following table were synthesized:

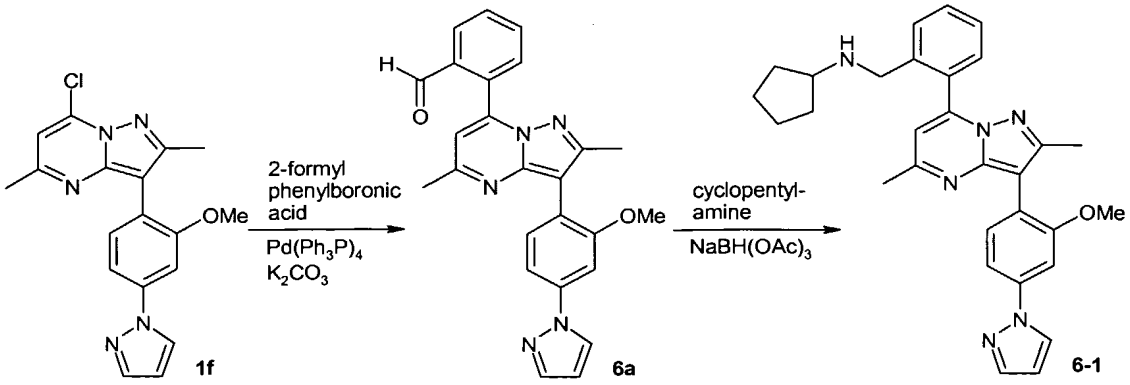


Cmpd	R_2	MW	MS	t_R*
5-1	$-C(O)N(CH_3)_2$	390.44		5.17
5-2	$-C(O)N(CH_2CH_3)_2$	418.50	419.2	6.22
5-3	$-C(O)N(CH_3)CH_2CH_3$	404.47	405.2	5.66

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 6

CYCLOPENTYL-{2-[3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-PYRAZOLO[1,5-A]PYRIMIDIN-7-YL]-BENZYL}-AMINE



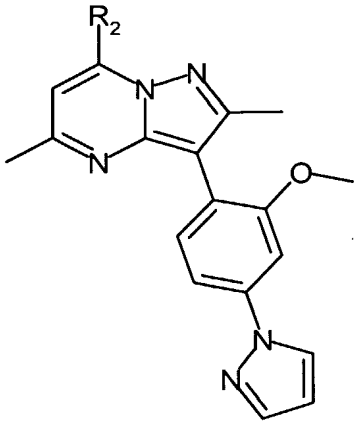
Step 6A:

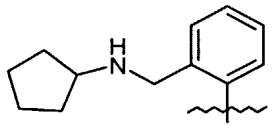
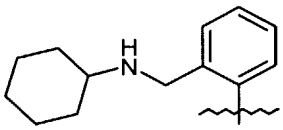
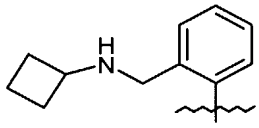
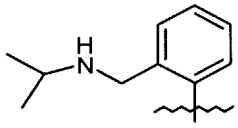
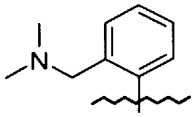
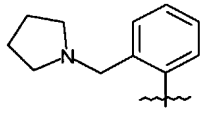
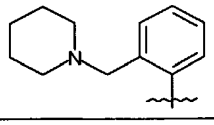
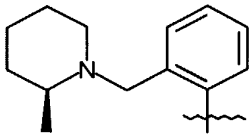
To a solution of **1f** (500 mg, 1.4 mmol, 1 eq) in 1:1 dioxane/water (6 mL) was added 2-formylphenylboronic acid (255 mg, 1.7 mmol, 1.2 eq), followed by potassium carbonate (390 mg, 2.8 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.07 mmol, 0.05 eq). The mixture was heated in a sealed tube at 100 °C for 3 hr, then the solvent was removed under vacuum. The residue was taken up in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, concentrated, and the residue was purified by silica gel column chromatography using 1:1 hexanes/ethyl acetate as eluent, to afford **6a** (500 mg, 85%) as a yellow solid.

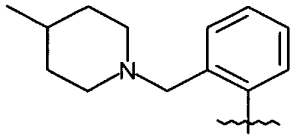
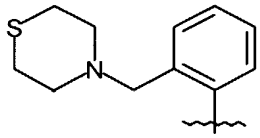
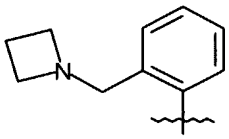
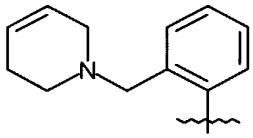
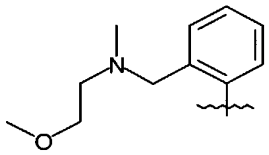
Step 6B:

Sodium triacetoxyborohydride (80 mg, 0.38 mmol, 2 eq) was added at RT to a solution of **6a** (80 mg, 0.19 mmol, 1 eq) and acetic acid (0.011 mL, 0.19 mmol, 1 eq) in dichloroethane (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing **6-1** (36 mg, 38 % yield) as a TFA salt.

Depending on the amine employed in the reductive amination step above, the compounds of the following table were synthesized:



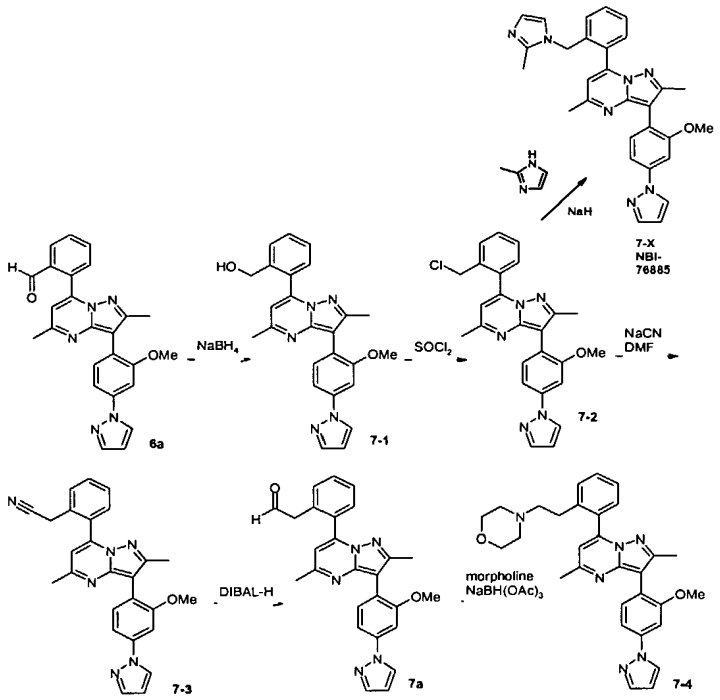
Cmpd	R_2	MW	MS	t_R*
6-1		492.62	493.4	5.69
6-2		506.65	507.4	5.95
6-3		478.60	479.1	5.49
6-4		466.59	467.1	5.33
6-5		452.559	452	4.40
6-6		478.597	478	4.70
6-7		492.624	492	4.85
6-8		506.651	506	4.74

Cmpd	R_2	MW	MS	t_R*
6-9		506.651	506	4.82
6-10		510.663	510	4.60
6-11		464.57	464	4.38
6-12		490.608	490	4.60
6-13		496.612	496	4.57

* All HPLC determinations employed Analytical Method 2.

EXAMPLE 7

3-(2-METHOXY-4-PYRAZOL-1-YL-PHENYL)-2,5-DIMETHYL-7-[2-(2-MORPHOLIN-4-YL-ETHYL)-PHENYL]-PYRAZOLO[1,5-A]PYRIMIDINE



Step 7A:

To a suspension of **6a** (345 mg, 0.82 mmol) in 1:1 THF/methanol (4 mL) at RT was added carefully sodium borohydride (62 mg, 1.6 mmol, 2 eq). The mixture was stirred for 30 min, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide **7-1** (450 mg, 90 %) as a solid, which was used without further purification.

Step 7B:

Thionyl chloride (0.17 mL, 2.3 mmol, 2.2 eq) was added to a solution of **7-1** (450 mg, 1.05 mmol, 1 eq) in DCM (5 mL) at RT. The mixture was stirred at RT for 30 min, then water was added and the mixture was extracted with DCM. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated to provide **7-2** (420 mg, 90 %) as a yellow solid.

Step 7-C

Sodium hydride (11 mg of 60 % dispersion in mineral oil, 0.28 mmol, 4 eq) was added to a solution of 2-Methylimidazole (17 mg, 0.21 mmol, 3 eq) in 2 ml DMF at rt. The mixture was stirred for 10 min, then a solution of 7-2 (30 mg, 0.07 mmol, 1 eq) in 0.2 ml DMF was added and the mixture was stirred at rt for 17 h. The mixture was diluted with methanol, then purified directly by preparative HPLC/MS, providing 7-X (6 mg) as a TFA salt.

Step 7D:

Sodium cyanide (3.3 mg, 0.067 mmol, 3 eq) was added to a solution of **7-2** (10 mg, 0.023 mmol, 1 eq) in DMSO (3 mL) at RT. The mixture was stirred at RT for 2 hr, then water was added and the mixture was extracted with DCM. The combined organic layers were washed with water and brine, then dried over sodium sulfate, filtered, and concentrated to provide crude **7-3** (8 mg, 80 % yield) as a solid.

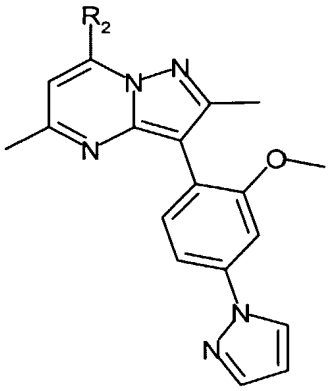
Step 7E:

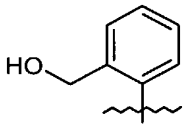
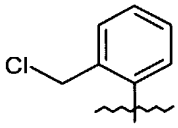
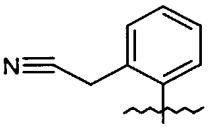
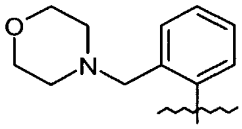
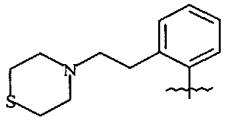
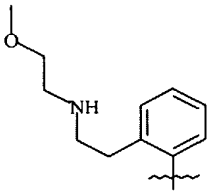
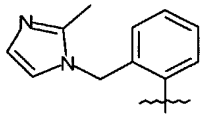
DIBAL-H (0.23 mL of a 1.5 M solution in toluene, 0.35 mmol, 3 eq) was added to a solution of **7-3** (50 mg, 0.11 mmol) in DCM (1 mL) at -78 °C. The mixture was stirred at –78 °C for 20 min, then was allowed to warm to RT. Water was added and the mixture was stirred for 10 min, then the aqueous layer was extracted with two additional portions of DCM. The combined organic extracts were washed with water and brine, were dried over sodium sulfate, filtered through Celite®, and concentrated. The residue was purified by prep HPLC/MS to provide **7a** (15 mg) as a TFA salt.

Step 7F:

Sodium triacetoxyborohydride (15 mg, 0.069 mmol, 2 eq) was added to a room temperature solution of **7a** (15 mg, 0.034 mmol, 1 eq) and acetic acid (0.002 mL, 0.034 mmol, 1 eq) in DCM (1 mL). The mixture was stirred at RT for 16 hr, then the mixture was concentrated, taken up in methanol, and purified directly by preparative HPLC/MS, providing **7-4** (11 mg, 50% yield) as a TFA salt.

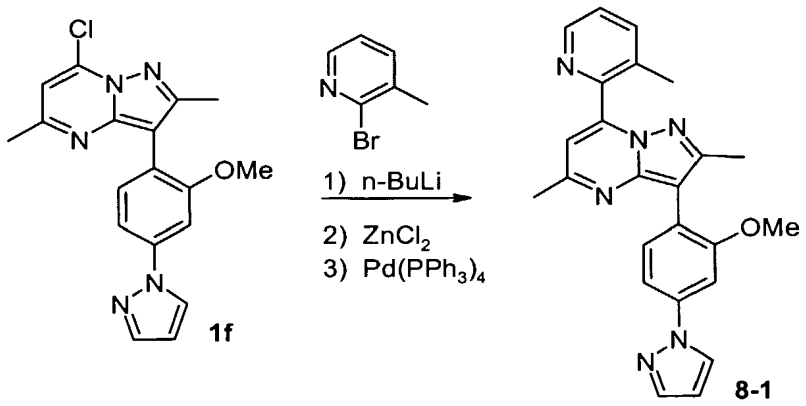
The following table summarizes the compounds of Example 7. By varying the amine employed in the reductive amination step above, Cmpds **7-5** and **7-6**, included in the table, were synthesized by the methods of Step 7E:



Cmpd	R_2	MW	MS	t_R	HPLC Method
7-1		425.49	425	5.41	2
7-2		443.94	444.1	1.15	4
7-3		434.50	435.4	7.05	2
7-4		506.82	509.2	5.13	2
7-5		524.69	525.2	5.48	2
7-6		496.612	497.2	5.18	2
7-7		489.58	490.2	4.94	

EXAMPLE 8

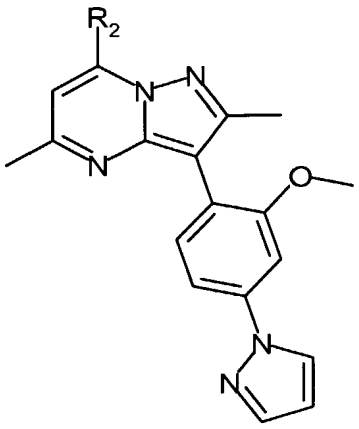
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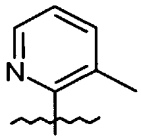
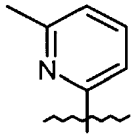
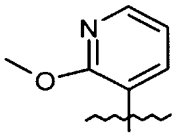
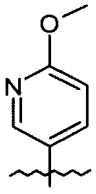
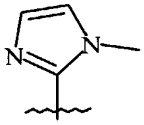
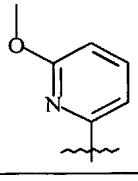
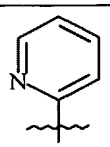


Step 8A:

To a solution of 2-bromo-3-methylpyridine (4.85 g, 28.2 mmol) in dry THF (8.0 mL) cooled to – 70 °C was added n-BuLi (1.6 M solution in hexane, 17.6 mL, 28.2 mmol) dropwise. The reaction mix was stirred at – 70 °C for 30 min, then $ZnCl_2$ (0.5 M solution in THF, 66.0 mL, 34 mmol) was added over 5 min. The mixture was allowed to warm to 0 °C over 1 hr, then Cmpd **1f** (1.66 g, 4.70 mmol) and tetrakis(triphenylphosphine)palladium(0) (326 mg, 0.28 mmol) were added. The mixture was then heated to reflux for 4 hr. The cooled reaction mixture was quenched with water, the THF was evaporated and the resulting aqueous mixture was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and the residue was chromatographed on silica gel using 1:3 hexanes/ethyl acetate to give **8-1** free base (1. 6 g, 83 %) as a yellow solid. To a solution of **8-1** (1.6 g, 3.9 mmol) in 7:1 ethyl acetate/chloroform (100 mL) was added hydrogen chloride (4.0 mL of a 2.0 M solution in ether, 8.0 mmol) at 0 °C. The suspension was diluted with ether, then the solid was collected on a fritted glass filter and rinsed with ether to obtain **8-1** HCl salt (1.7 g, 98 %) after drying under high vacuum.

Depending on the halide employed in Step 8A above, the compounds of the following table were synthesized:



Cmpd	R_2	MW	MS	t_R*
8-1		410.48	411	5.400
8-2		410.48	411	5.770
8-3		426.48	427	5.690
8-4		440.51	441	6.240
8-5		399.456	399	4.130
8-6		426.478	426	6.410
8-7		396.452	396	5.720