



Progress in corticotropin-releasing factor-1 antagonist development

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Corticotropin releasing factor (CRF) receptor antagonists have been sought since the stress-secreted peptide was isolated in 1981. Although evidence is mixed concerning the efficacy of CRF₁ antagonists as antidepressants, CRF₁ antagonists might be novel pharmacotherapies for anxiety and addiction. Progress in understanding the two-domain model of ligand–receptor interactions for CRF family receptors might yield chemically novel CRF₁ receptor antagonists, including peptide CRF₁ antagonists, antagonists with signal transduction selectivity and nonpeptide CRF₁ antagonists that act via the extracellular (rather than transmembrane) domains. Novel ligands that conform to the prevalent pharmacophore and exhibit drug-like pharmacokinetic properties have been identified. The therapeutic utility of CRF₁ antagonists should soon be clearer: several small molecules are currently in Phase II/III clinical trials for depression, anxiety and irritable bowel syndrome.

Corticotropin releasing factor (CRF) receptor antagonists have been sought since Vale *et al.* isolated the stress-secreted, adrenocorticotropin-releasing hypothalamic peptide in 1981 [1]. The identification of CRF was followed by the discovery of genes encoding three paralogs of CRF (urocortins 1, 2 and 3; Ucn 1, Ucn 2 and Ucn 3) and two G-protein-coupled receptors (CRF₁ and CRF₂) that the CRF/Ucn peptides bind and activate with varying affinities [2,3]. Pharmacological and transgenic studies show that brain and pituitary CRF₁ receptors mediate endocrine, behavioral and autonomic responses to stress [4]. Consequently, the pharmaceutical industry has sought to develop blood–brain-barrier-penetrating, selective CRF₁ receptor antagonists [5]. Previous reviews by us and others have surveyed the biology of CRF systems [2]; the pharmacophore, physiochemical properties and pharmacokinetics of prototypical nonpeptide CRF₁ receptor antagonists [6–9]; and the therapeutic potential of CRF₁ antagonists for stress-related indications [6,10,11], including major depression [12], anxiety disorders [13] and irritable bowel syndrome [14]. This article, after briefly overviewing the CRF/Ucn system and preclinical data supporting the therapeutic potential of CRF₁ antagonists for anxiety, depression and addictive disorders, reviews advances in CRF₁ antagonist development since 2005.

Biology of CRF/Ucn receptor systems

CRF-related peptides interact with two known mammalian CRF receptor subtypes, CRF₁ and CRF₂, which both belong to the class B1 (secretin-like) subfamily of G-protein-coupled receptors. The CRF₁ receptor exists in multiple isoforms (e.g. CRF_{1a}–CRF_{1h}), with the best known and functional isoform the CRF_{1(a)} subtype. The CRF₂ receptor has three known functional membrane-associated subtypes in humans – CRF_{2(a)}, CRF_{2(b)} and CRF_{2(c)} – and a ligand-sequestering, soluble CRF_{2(a)} isoform discovered in mouse. CRF₁ and CRF₂ receptors have ~70% sequence identity. CRF has high, preferential affinity for CRF₁ versus CRF₂ receptors. Ucn 1 is a high-affinity agonist at both receptors, and the type 2 urocortins (Ucn 2 and Ucn 3) are more selective for membrane do CRF₂ receptors. The biological actions of CRF, Ucn 1 and Ucn 2 in rodents are also modulated by a CRF-binding protein (CRF-BP), a 37-kDa secreted glycoprotein that binds and putatively immunosequesters CRF and Ucn 1 with equal or greater affinity than CRF receptors. Structural requirements for binding to CRF receptors and the CRF-BP differ. Many (if not most) CRF receptor antagonists do not bind the CRF-BP [3,6].

CRF₁ receptors mediate not only the hypothalamic-pituitary-adrenal (HPA) axis neuroendocrine response to stress but also other aspects of stress responses in organisms. The distribution of CRF₁ receptors in the brain is highly conserved in stress-responsive

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brain regions, including the neocortex, central extended amygdala, medial septum, hippocampus, hypothalamus, thalamus, cerebellum, and autonomic midbrain and hindbrain nuclei. This receptor distribution, concordant with that of its natural ligands CRF and Ucn 1, is consistent with the recognized role for extrahypothalamic CRF₁ receptors in behavioral and autonomic stress responses.

CRF₁ antagonists in animal models of anxiety, depression and addictive disorders

Nonpeptide CRF₁ antagonists consistently produce anxiolytic-like effects in animal models [6]. For example, in rodents, the compounds reduced conditioned fear [15,16], shock-induced freezing [17], anxiety-like responses to neonatal isolation [18,19] and defensive burying behavior [20,21]. CRF₁ antagonists reduced acoustic startle responding [22,23] and showed efficacy in exploration-based models of anxiety, such as the open field, elevated plus maze, light–dark box and defensive withdrawal tests [18,24–27], under stressed, but not nonstressed, testing conditions. CRF₁ antagonists only exhibited weak activity in punished drinking and punished crossing conflict models (unlike γ -aminobutyric acid anxiolytics) [18,28] but effectively increased social interaction [28,29]. In rodents, little tolerance to the anxiolytic-like actions of CRF₁ antagonists is observed with daily administration for up to 14 days [6]. CRF₁ antagonists also blocked pain-related synaptic facilitation and anxiety-like behavior [30,31]. In addition, the compounds produced anxiolytic-like effects in intruder tests using nonhuman primate models [32,33].

Despite initial positive results, however, data with small-molecule CRF₁ antagonists have not consistently shown efficacy in animal models that predict antidepressant activity [5]. Regarding positive findings, subchronic treatment with DMP696 and R121919 reduced forced swim immobility in mice [34], and chronic treatment with SSR125543 increased swimming in Flinder Sensitive Line rats, a putative genetic model of depression [35]. Acute antalarmin treatment similarly reduced forced swim immobility in CRF₂-receptor-null mutant mice [36], and antalarmin, SSR125543A, LWH234 and CRA1000 acutely reduced immobility in some, but not all, studies of outbred rats [18,37,38]. R278995 reduced hyperemotionality of olfactory bulbectomized rats [39], a putative model of depression [40]. Chronic treatment with antalarmin or SSR125543A also improved coat appearance and reversed reductions in hippocampal neurogenesis in a mouse model of chronic mild stress [18,41,42].

Regarding negative findings, R121919, CP-154526 and R278995 failed to reduce forced swim immobility in rats [38,39], and antalarmin, CP-154526, DMP904, R121919 and DMP696 failed to reduce forced swim immobility in mice after acute, subchronic or chronic (16 days) dosing [34,43,44]. Furthermore, antalarmin, CP-154526, DMP904, R121919, DMP696 and R278995 were all inactive in the tail suspension test with acute dosing [34,39,45]. Although acute treatment with CP-154526 was first reported to produce antidepressant-like effects in the learned helplessness paradigm [46], a subsequent study with CP-154526 failed to replicate this finding [47]. DMP904, DMP696 and CRA1000 were also inactive in this model after acute dosing [47,48]. Nonetheless, CP-154526, CRA1000 and R278995 prevented the acquisition, but not the expression, of learned helplessness [39,47,49]. R278995

did not produce antidepressant-like effects in the rat differential-reinforcement-of-low-rate 72-s model [39]. A potential explanation for these mixed findings is that CRF₁ antagonists might only exhibit antidepressant-like activity in ‘dysfunction’ models or models that exhibit a depressive-like endophenotype as a result of the animals’ genetic background or environmental manipulation (e.g. olfactory bulbectomy) and not in healthy, normal animals. Such an interpretation is consistent with findings showing that CRF₁ antagonists differentially reduce anxiety-like behavior in models of high anxiety [6] and reduce drug or ethanol intake in models of dependence [50–58], rather than in healthy, nondependent animals; however, this interpretation might be difficult to reconcile with the inability of CRF₁ antagonists to reproducibly reverse learned helplessness behavior that results from repeated inescapable shock. A better understanding of the preclinical conditions under which CRF₁ antagonists exert antidepressant-like effects might have translational implications for identifying patient subgroups or conditions under which CRF₁ antagonists are more likely to be clinically useful for depression.

Another major action of CRF₁ antagonists has been in the context of the activation of brain stress systems in addiction. As reviewed recently [59], both conceptual and neurobiological advances suggest that CRF₁ systems contribute to the withdrawal–negative affect and preoccupation–anticipation (craving) stages of the addiction cycle that fuel compulsive drug taking. Regarding the withdrawal–negative affect stage, dysphoria and increased anxiety are associated with both acute and protracted abstinence from most drugs of abuse. Such negative emotional symptoms, via negative reinforcement, drive high levels of drug taking to prevent or relieve the aversive withdrawal state, which is hypothesized to be mediated by CRF₁ activation. Consistent with this hypothesis, both the HPA axis and extrahypothalamic CRF systems are activated during acute withdrawal from all major drugs of abuse in animal models [60], and central infusion of nonpeptide CRF antagonists block the anxiogenic-like responses observed during acute withdrawal from drugs of abuse, including cocaine, alcohol, nicotine and cannabinoids [61]. Similarly, systemic administration of blood–brain-barrier-penetrating CRF₁ antagonists reduced the anxiogenic-, aversive- and hypohedonic-like effects of withdrawal from opioids [62–65], nicotine [56,66], benzodiazepines [63] and alcohol [29,54,55,67,68]. Supporting the motivational significance of withdrawal-associated CRF₁ system activation for drug taking, administration of small-molecule CRF₁ antagonists also reduced the excessive drug intake associated with dependence on alcohol [50–55,69], nicotine [56], cocaine [57] and opioids [58]. Relatedly, CRF₁ antagonists might also have therapeutic potential in individuals who self-medicate innate negative emotional states by taking excessive amounts of drugs or alcohol. This claim is supported by the anti-drinking efficacy of small-molecule CRF₁ antagonists selectively in rats that show high innate anxiety, such as Marchigian alcohol-preferring rats [70] and isolation-reared Fawn-Hooded rats [71].

Stress is a major recognized precipitant of relapse, and CRF₁ antagonists, therefore, are also hypothesized to have therapeutic potential in the ‘craving’ stage of the addiction cycle by preventing stress-induced relapse. Accordingly, nonpeptide CRF antagonists centrally block stress-induced reinstatement of drug-seeking behavior in animal models [72]. Similarly, systemic administration of

small-molecule CRF₁ antagonists reduced footshock stress-induced reinstatement of heroin-, cocaine-, nicotine- or alcohol-seeking behavior in rats [55,66,73–75] and footshock stress-induced reactivation of conditioned place preference for opioids and cocaine [76,77]. Thus, models of drug withdrawal, excessive drug taking, innate anxiety with comorbid ethanol intake and stress-induced relapse behavior all support the therapeutic potential of CRF₁ antagonists for drug dependence.

Peptide CRF₁-selective receptor antagonists

Several N-terminally truncated and substituted analogs of CRF act as subtype nonselective competitive partial agonists or full antagonists at CRF receptors. Examples of these, in chronological order of discovery, include the partial agonist [Met¹⁸, Lys²³, Glu^{27,29,40}, Ala^{32,41}, Leu^{33,36,38}] r/hCRF_{9–41} (α-helical CRF_{9–41}) and the full receptor antagonists [D-Phe¹², Nle^{21,38} CaMeLeu³⁷] r/hCRF_{12–41} (D-Phe CRF_{12–41}), cyclo(30–33) [D-Phe¹², Nle^{21,38}, Glu³⁰, Lys³³] r/hCRF_{12–41} (astressin) and cyclo(30–33) [D-Phe¹², Nle²¹, CaMeLeu²⁷, Glu³⁰, Lys³³, Nle³⁸, CaMeLeu⁴⁰]Ac-r/hCRF_{9–41} (astressin-B). These peptide ligands have approximately the same order of binding and antagonist potency at CRF₁ versus CRF₂ receptors and do not cross the blood–brain barrier. Thus, they are subtype nonselective, peripherally acting CRF receptor antagonists.

An emerging development within the past five years is that in the course of seeking minimal fragments of CRF that retain antagonist activity, CRF₁-preferring peptide antagonists might have been identified. Yamada *et al.* [78] followed up a Solvay patent application [79] that described a peptide comprising the 12 C-terminal residues of astressin as a potent antagonist of CRF receptors. Through amino acid substitution of Nle³⁸ with a lipophilic cyclohexylalanine residue and Ala³¹ with an unnatural residue (D-Ala), they identified a metabolically stable, high-affinity (*K_i* ~3 nM) CRF₁ antagonist that potently (0.1 mg/kg, i.v.) reduced adrenocorticotrophic hormone secretion in a rat sepsis model. This peptide might be a CRF₁-preferring antagonist; the Solvay group concurrently reported that the 12-residue N-terminal truncated astressin derivative from which Yamada and colleagues began their studies retains CRF₁ affinity but is inactive at the CRF_{2(a)} receptor. Thus, lactam-bridge-constrained N-terminally truncated astressin derivatives of 12–15 residue length might be preferential CRF₁ receptor peptide antagonists. Such compounds could be useful for the treatment of pathologies associated with peripheral CRF₁ hyperactivation [80], perhaps including irritable bowel syndrome, premature labor, postoperative gastric ileus, and Cushingoid aspects of severe alcohol dependence, visceral obesity, melancholic major depression and anorexia nervosa [5].

Progress in the two-domain model of ligand–CRF₁ receptor interaction

Progress has also been made in understanding the mode of ligand–CRF₁ receptor interaction. Natural peptide agonists of CRF receptors are thought to bind and activate the receptor via a two-site mechanism. The carboxyl end of the agonist first binds the N-terminal first extracellular domain (ECD1) (N-domain), and the amino portion of the ligand successively binds the extracellular face of the seven juxtamembrane regions (J-domain), stabilizing an agonist-bound, ‘active’ receptor state that yields signal transduction [81,82]. Interaction with the J-domain might also be impor-

tant for receptor internalization because short (e.g. 12-residue) C-terminal peptide antagonists that only bind the N-domain do not trigger endocytosis, unlike longer antagonists that also interact with the J-domain (e.g. astressin) [83].

Recently, a minimal cyclic peptide fragment homologous to the 12 C-terminal residues of astressin was used to understand determinants of ligand binding to the N-domain of the CRF₁ receptor recombinantly isolated from the J-domain [84]. NMR spectroscopy showed that two hydrophobic residues (Met³⁸ and Ile⁴¹ of CRF sequence) and two amide groups (Asn³⁴ and the C-terminal amide) on one face of the bound peptide’s α helix defined the antagonist’s binding epitope. This epitope could potentially be used as a template to develop novel nonpeptide competitive antagonists that target the agonist-binding N-domain of the CRF₁ receptor, in contrast to existing small-molecule antagonists that allosterically target the J-domain [82].

Recently, different ligands have been shown to address the J-domain of the receptor differently, conferring not only receptor subtype selectivity but also signal transduction pathway selectivity within a given receptor subtype. For example, the NMR solution structures of astressin-B, astressin₂-B and Ucn 2 exhibit a large (90°) kink that, after binding to the N-domain, orients the ECD1 with its positively charged face toward the negatively charged extracellular loops 2–4 of the receptor. By contrast, astressin, stressin₁, hUcn1 and hUcn3 have no or much smaller kinks, such that the ECD1 of the receptor would have to orient at a different angle to enable ligand interaction with the J-domain. Grace *et al.* hypothesized that the different ligand–receptor complex conformations could lead to the engagement of different signal transduction pathways [85]. Supporting this hypothesis, single substitutions of Ucn 1 with bulky amino acids (e.g. benzoyl-phenylalanine or naphthylalanine) in residues 6–15, but not at other positions, eliminated the peptide’s ability to stimulate G_i-protein activation while not altering its activation of G_s-protein pathways. The resulting analogs were competitive receptor antagonists for the G_i-protein pathway and agonists for the G_s pathway [86]. Similarly, the nonpeptide antagonist antalarmin, which binds the J-domain of the receptor, had different antagonist potency against urocortin- versus sauvagine-induced G-protein activation and also exhibited different modes of antagonist action: competitive for receptor coupling to G_s but noncompetitive for G_i activation. By contrast, the peptide antagonist α-helical CRF_{9–41}, which binds the peptide agonist-binding N-domain, uniformly and competitively antagonized urocortin- or sauvagine-induced activation of both G_i and G_s signaling pathways [87]. These results suggest that antagonism of specific CRF₁ signal transduction pathways might be possible via ligands that stabilize or destabilize particular ligand–receptor complex conformations.

A final recent finding regarding the mode of CRF antagonist action was that nonpeptide ligands can allosterically facilitate or inhibit binding of CRF to G-protein-uncoupled CRF₁ receptors while uniformly inhibiting signaling efficacy in the CRF-bound, active, G-protein-coupled state. Positive and negative allosteric modulators of CRF affinity for the uncoupled receptor functioned as intrinsic weak agonists and inverse agonists at uncoupled receptors, respectively. Thus, different conformational states can lead to the inhibition of CRF signaling. Nonpeptide ligands can act as functional antagonists by stabilizing an inactive (allosteric

inverse agonist) or weakly active (allosteric agonist) receptor state, either of which can shift receptor equilibrium away from the CRF-bound, fully active signaling state [88].

Novel, nonpeptide CRF₁-selective receptor antagonists Pharmacophore and selectivity

Since 2005, many small molecules with high and selective CRF₁ (versus CRF₂) affinity have been identified (Table 1). Each series follows the previously reviewed general pharmacophore common to most nonpeptide CRF₁ antagonists. Prototypical compounds (Figure 1) share one or two aliphatic top units that occupy a hydrophobic pocket of the receptor, a central mono-, bi- or tricyclic ring core and an orthogonal, conformation-stabilizing 2,4-di- or 2,4,6-tri-substituted aromatic bottom group. Each ring core contains a putative proton-accepting ring nitrogen separated from the pendant aromatic by a one- or, more commonly, two-atom spacer. The core ring is typically methylated on the opposite position adjacent to the bonding nitrogen. The hydrogen-bond-accepting core nitrogen is hypothesized to interact with the imidazole side chain of histidine-199, a polar amino acid in the third

transmembrane domain of the CRF₁ receptor that is not shared in the CRF₂ receptor or CRF-BP sequences. Nonpeptide antagonists of this pharmacophore also require the rotational flexibility present in methionine residue 276 of the CRF₁ (and not CRF₂) receptor sequence [89], putatively to permit a hydrophobic interaction of the ring core with the fifth transmembrane domain. Accordingly, mutation of the 199 or 276 CRF₁ residues (His-199, Met-276) to their corresponding CRF₂ amino acids (Val-199, Ile-276) reduced the binding affinity of the selective CRF₁ antagonist NBI 27914 by 40- and 200-fold, respectively [90]. A computational model incorporating both structural interaction features recently yielded good affinity predictions for a series of dihydropyridopyrazinone and dihydropteridinone CRF₁ antagonists ($r^2 = 0.71$) [91]. An independent *in silico* receptor docking model reached a similar conclusion regarding the structural mode of antagonist action for dihydropyrrolo[2,3-*d*]pyrimidines [92]. Thus, nonpeptide antagonists of the prevalent pharmacophore seem to be potent and selective CRF₁ antagonists partly in relation to their interactions with features in the third (His-199) and fifth (Met-276) transmembrane receptor domains.

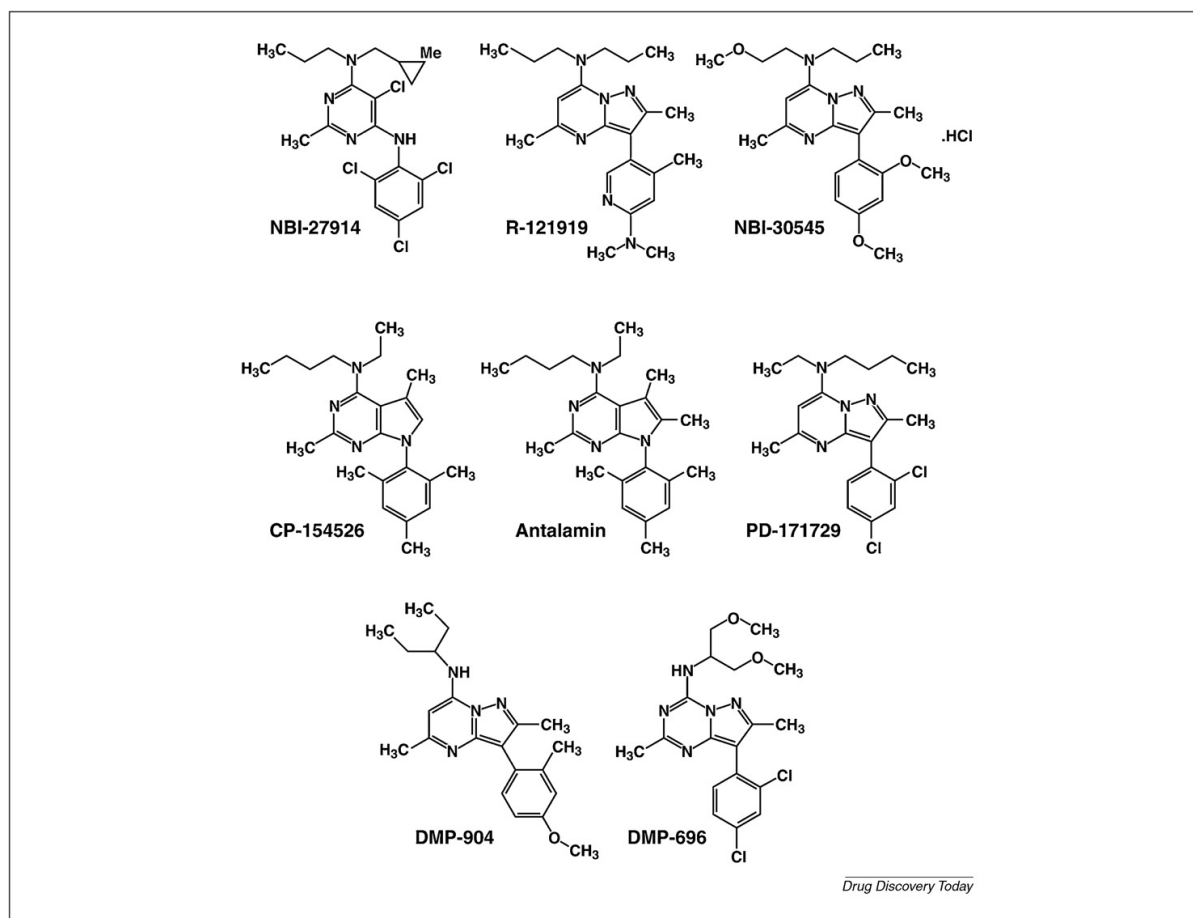


FIGURE 1

Prototypical CRF₁ antagonists.

TABLE 1
Selected novel nonpeptide CRF₁ antagonists in recent peer-reviewed literature (2005–2009)^a

Company	Core Best cycles exemplars	CAS registry	CRF ₁ affinity (nM)	pK _a	c log P	c log D _{pH=7}	c log D _{pH=2}	MW	PSA (Å)	Oral bioavailability (%)	C _p plasma (ml/min kg)	V _d (L/kg)	t _{1/2} (h)	Notes	Refs
Neurogen	Bi	26k	1012325-20-0 K _d = 8	5.84	7.54	7.52	5.07	448.5	25.4	4.8	14.5	13	5.4	–	[100]
	Mono	12b	1067229-15-5 K _d = 9	–	5.00	–	–	380.9	–	6	13.6	14	8	–	[101]
	Neurocrine	Mono	7r	848648-99-7 K _d = 7	4.65	7.17	7.17	4.85	445.0	43.2	84	27.7	7.8	3.3	B/P = 0.20
Neurocrine	Tri	19g	374798-46-6 K _d = 3.5	9.34	8.37	6.25	5.87	396.0	21.1	24	70	38	6.3	B/P = 0.27; reduced restraint-induced ACTH (10 mg/kg)	[103]
Neurocrine	Tri	22a	877672-44-1 K _d = 2.9	13.41	5.43	3.43	2.43	419.4	31.2	7	43	44	12	B/P = 0.53; reduced restraint-induced ACTH (10 mg/kg)	[103]
Neurocrine	Tri	16g	268539-94-2 K _d = 2	10.78	2.45	-0.03	-0.05	394.5	48.9	30	53	7.2	1.6	B/P = 2.8; reduced i.v. CRF-induced ACTH (10 mg/kg)	[94]
Neurocrine	Tri	12a (NB135965)	603151-83-3 K _d = 3 (free base)	7.91	5.14	4.19	2.64	401.3	29.0	34	17	17.8	12	B/P = 1.25; reduced restraint or i.v. CRF-induced ACTH (10–20 mg/kg, p.o.); blocked i.c.v. CRF-induced colonic motility	[104]
Neurocrine	Tri	12t (NB134041)	268545-87-5 K _d = 4	7.91	6.22	5.27	3.72	417.4	29.0	–	–	–	–	Reduced footshock or i.v. CRF-induced ACTH (3 mg/kg)	[104,105]
GSK	Tri	2ba	862901-68-6 IC ₅₀ = 14	6.78	6.82	6.25	4.33	484.5	34.0	33	10	–	–	B/P = 1.3; MED = 30 mg/kg p.o. in rat pup ultrasonic vocalization model	[106]
	Tri	3a	476645-12-2 IC ₅₀ = 100	9.86	8.49	6.15	5.99	483.5	21.1	71	8	2.5	5.3	–	[107]
GSK	Bi	3ac	474655-90-8 IC ₅₀ = 174	7.19	6.4	5.99	3.90	390.3	29.0	22	41	5.4	3.1	B/P = 0.35	[7]
GSK	Bi	4fi	474657-07-3 IC ₅₀ = 48	1.84	3.53	3.30	3.30	414.2	46.8	86	9	3.3	6	B/P = 2.30; ED ₅₀ = 2.0 mg/kg p.o. in rat pup ultrasonic vocalization model	[7]
GSK	Bi	2a	474655-69-1 IC ₅₀ = 32	0.79	6.04	6.04	6.01	496.4	88.0	52	12	3.7	5.1	B/P = 2.30; ED ₅₀ = 10.0 mg/kg p.o. in rat pup ultrasonic vocalization model	[108]
GSK	Bi	27	727992-91-8 IC ₅₀ = 35	3.93	3.07	3.07	1.23	439.5	84.3	–	–	–	–	–	[92]
GSK	Bi	3	786701-83-5 IC ₅₀ = 66 (GW876008)	4.81	1.54	1.54	-0.79	402.4	75.5	66	19	2.4	1.6	B/P = 3.7; reduced i.c.v. CRF-induced gerbil forepaw treading (10 mg/kg), marmoset defensive postures (10 mg/kg), rat pup ultrasonic vocalization (30 mg/kg)	[95]
Pfizer	Mono	19	675198-68-2 K _d = 11	1.46	3.85	3.85	3.65	436.5	69.2	–	–	–	–	–	[109]
Pfizer	Mono	2 (CP-316311)	175139-41-0 IC ₅₀ = 7	5.63	6.20	6.18	3.73	327.5	31.4	3.6 (fasted), 37 (fed)	4.1	1.1	8.3	Reduced i.v. CRF-induced ACTH (10 mg/kg), defensive withdrawal (10 mg/kg), fear-potentiated startle (32 mg/kg, p.o.)	[96]
Pfizer	Mono	3a	175140-00-8 IC ₅₀ = 5	7.23	7.33	6.9	4.83	326.5	34.2	22 (fasted), 64 (fed)	17	5.3	8.8	Reduced i.v. CRF-induced ACTH and fear-potentiated startle (10 mg/kg, p.o.)	[97]

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TABLE 1 (Continued)

	Company	Core cycles	Best exemplars	CAS registry	CRF ₁ affinity (nM)	pK _a	c log P	c log D _{PH+7}	c log D _{PH+2}	MW	PSA (A)	Oral bioavailability (F%)	C plasma (ml/min kg)	V _d (L/kg)	t _{1/2} (h)	Notes	Refs
7-Aryl-6,7-dihydroimidazoimidazole	BMS	Bi	7b	444321-96-4	K _d = 42	6.66	3.68	3.52	1.18	394.5	41.4	32	35	5.7	–	B/P = 0.21; anxiolytic-like activity in mouse canopy model (32 mg/kg)	[110]
Imidazo[1,2-b]benzimidazoles	BMS	Tri	8e	444323-42-6	K _d = 23	7.93	8.34	–	–	468.6	25.5	35	5.1	0.6	4.1	B/P = 0.3	[111]
8-Aryl-1,3a,7,8-tetraaza-cyclopental[<i>d</i>]indenes	BMS	Tri	9d	444324-30-5	K _d = 7.8	8.45	7.14	–	–	451.6	38.4	4	5.2	0.5	3	Anxiolytic-like activity in mouse canopy model (30 mg/kg)	[112]
2-Anilino-3-phenylsulfonyl-6-methylpyridines	BMS	Mono	7f	777940-17-7	K _d = 52	2.53	6.86	6.86	6.22	394.5	67.4	35	5.2	25	5.1	–	[113]
Dihydropyridopyrazinones	BMS	Bi	2a	795300-31-1	IC ₅₀ = 0.8	5.46	3.10	3.09	0.63	399.5	79.8	–	–	–	–	–	[91]
Dihydropteridines	BMS	Bi	2d	937723-70-1	IC ₅₀ = 10	4.92	3.69	3.69	1.48	386.5	75.6	–	–	–	–	–	[91]
Imidazo[1,2-b]pyridazine	Eli Lilly/ NIAAA	Bi	MTIP	910551-43-8	K _d = 0.22	3.96	3.55	3.55	1.64	420.0	83.8	91	4.9	1.7	3.9	Reduced conflict behavior; reduced 'hangover' anxiety-like behavior in elevated plus-maze (10 mg/kg); reduced ethanol self-administration (10 mg/kg); reduced ethanol-seeking behavior in ethanol post-dependent or alcohol-preferring rats	[54,55]
Pyrazolo[1,5-a]pyrimidine	Scripps (Dupont/BMS composition patent)	Bi	MPZP	202579-76-8	K _d = 4.9	5.32	2.95	2.93	0.50	398.5	61.1	–	–	–	–	Reduced defensive burying behavior; reduced ethanol, nicotine and cocaine self-administration in dependence models	[52,53,56,57]
8-(4-Pyrid-3-yl)pyrazolo[1,5-a]-1,3,5-triazines	BMS	Bi	13-15 Pexacerfont (BMS-562,086)	459856-18-9	K _d = 6.1	2.99	2.94	2.94	1.66	340.4	77.2	40	17.9	14.9	13.5	Anxiolytic-like activity in elevated plus-maze and defensive withdrawal models (10 mg/kg, p.o.); observed log P = 4.32; solubility of 16 µg/ml in water (pH 7.4) and 16.3 mg/ml in 0.01 N HCl (pH 2.5); good pharmacokinetics in nonhuman primates	[98]
8-(4-Methoxyphenyl)pyrazolo[1,5-a]-1,3,5-triazines:	BMS	Bi	6 in 1st in 2 nd (BMS-561,388)	202578-88-9 (free base)	K _d = 4.7	6.63	2.15	1.99	-0.35	399.5	74.0	51	20	14.6	9.7	Anxiolytic-like activity in elevated plus-maze and defensive withdrawal models (10 mg/kg, p.o.); observed log P = 4.76; solubility < 1 µg/ml in water (pH 7.4) and 2.5 mg/ml in 0.01 N HCl (pH 2.5); inferior oral pharmacokinetics in chimpanzee compared with Pexacerfont	[98,114]

Abbreviations: ACTH, adrenocorticotrophic hormone; B/P, brain/plasma ratio; c log P, calculated log P; c log D, calculated log D at specified pH; CRF, corticotropin-releasing factor; MW, molecular weight; NIAAA, National Institute on Alcohol Abuse and Alcoholism; pK_a, negative log of the acid-dissociation constant; PSA, polar surface area.

^a Intravenous pharmacokinetic parameters include C_i (clearance from plasma), V_d (volume of distribution at steady state) and t_{1/2} (plasma half-life). Physicochemical properties were calculated using Advanced Chemistry Development (ACD/Labs) Software v. 8.19 for Solaris.

TABLE 2
Recent clinical trials for CRF₁ antagonists

Company	Compound	Stage	Date initiated	Current status	Trial description	Reference compound	Clinicaltrials.gov or other identifier
GlaxoSmithKline/ Neurocrine	GW876008	Phase I	Nov 2006	Completed	Metabolism in smokers versus nonsmokers	–	NCT00429728
	GW876008	Phase I	Dec 2006	Completed	Safety study; potential interaction with midazolam	–	NCT00423761
	GW876008	Phase I	Mar 2007	Completed	fMRI of emotional processing in healthy volunteers	Lorazepam	NCT00424697
	GW876008	Phase I	Jun 2007	Terminated	Effects on pharmacokinetics of oral contraceptives	–	NCT00508911
	GSK561579	Phase I	Oct 2006	Completed	Effects on metyrapone-induced ACTH secretion	Alprazolam	NCT00426608
	GSK561579	Phase I	Oct 2007	Completed	Variability in absorption study	–	NCT00539136
	GSK561579	Phase I	Sep 2007	Recruiting	fMRI of emotional processing in healthy volunteers	Lorazepam	NCT00513565
	GSK561679 and GW876008	Phase I/IIa	Nov 2006	Completed	fMRI of regional cerebral blood flow in IBS patients	–	NCT00376896
	GW876008	Phase I/IIa	Aug 2007	Terminated	Endocrine responses to meals in IBS patients	–	NCT00511563
	GW876008	Phase IIa	Dec 2006	Completed	Gut blood flow and pain sensitivity in IBS patients	–	NCT00385099
BMS	GW876008	Phase II	Nov 2006	Completed	Multi-site, double-blind, placebo-controlled study in IBS patients	–	NCT00421707
	GSK561679 and GW876008	Phase I/IIa	Mar 2007	Completed	fMRI response to public speaking in social anxiety disorder	Alprazolam	NCT00555139
	GW876008	Phase II	Nov 2006	Completed	Multi-site, double-blind, placebo-controlled study in social anxiety disorder	Paroxetine	NCT00397722
	GSK561679	Phase II	Oct 2008	Recruiting	Multi-site, double-blind, placebo-controlled study in major depression	–	NCT00733980
	GSK586529	Phase I	–	Completed	Single-dose, escalating trial toward anxiety and depression indications	–	www.neurocrine.com/ 3rd quarter, 2008 release
	Pexacerfont (BMS-562,086)	Phase II/III	Jul 2007	Completed	Multi-site, double-blind, placebo-controlled study in generalized anxiety disorder	Escitalopram	NCT00481325
	Pexacerfont (BMS-562,086)	Phase I/II	Nov 2005	Completed	Multi-site, double-blind, placebo-controlled study in major depression	Escitalopram	NCT00135421
	Pexacerfont (BMS-562,086)	Phase II	Dec 2006	Completed	Multi-site, double-blind, placebo-controlled study in IBS patients	–	NCT00399438
	BMS-561,388	Phase I	2003–2004	Uncertain	Effects on reproductive hormones and menstrual cycle in young healthy women	–	http://myprofile.cos.com/miss_kc02
	CP-316,311	Phase II	Apr 2005	Terminated Mar 2006 (negative results)	Multi-site, double-blind, placebo-controlled study in major depression	Sertraline	NCT00143091
Ono	PF-57,2778	Phase I	–	Terminated	Safety study toward generalized anxiety disorder indication	–	–
Ono	ONO-2333Ms	Phase II	Jun 2007	Terminated Jul 2008 (negative results)	Multi-site, double-blind, placebo-controlled study in recurrent major depression	–	NCT00514865
Taisho/Janssen (Johnson&Johnson)	TAI-041/JNU-19567470	Phase I	Dec 2004	Uncertain	–	–	–
Sanofi-Aventis	SSR 125543	Phase I	–	Uncertain	–	–	http://en.sanofi-aventis.com/research_innovation/rd_strategy/cns/cns.asp (Feb 2008)
Neurocrine	NBI-34101	Phase I	–	–	–	–	–
NIH	Antalarmin	Preclinical	–	–	Completed pre-Phase I toxicity studies	–	[115]

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Previously reviewed compounds that depart considerably from the pharmacophore include oxo-7H-benzo[e]pyrimidine-4-carboxylic acid derivatives (subtype nonselective CRF receptor antagonists discovered by Alanex), CC 2064460 (a moderately potent arylamidrazone CRF₁ antagonist that lacks a central ring core with the customary hydrogen-bond-accepting nitrogen) and stereospecific N-phenylphenylglycines (which also lack a ring core but were identified through computational screening based on a classic pharmacophore training set [6]).

Lipophilicity and pharmacokinetic properties

As we and others have reviewed previously, clinical development of nonpeptide CRF₁ antagonists has been hampered because most leads were undesirably lipophilic, with poor water solubility and pharmacokinetic properties [6,9]. Most early CRF₁ antagonists failed Lipinski's 'rule of five' criteria for drug candidates because of excessive lipophilicity ($c \log P > 5$). This benchmark is relevant because of more than 100 drugs marketed as of 1992 for CNS indications, not one had a $\log D > 4$, which can yield poor physiochemical and pharmacokinetic properties. Rather, most (~85%) had a $\log D$ of 0–3. Preclinical studies since 2005, therefore, have sought to identify less hydrophobic, more drug-like CRF₁ antagonists with favorable pharmacokinetic properties and fewer anticipated toxicities.

Table 1 shows pharmacological, physiochemical and pharmacokinetic properties of several nonpeptide CRF₁ receptor antagonists from recent peer-reviewed literature (2005–2008). Many exemplar antagonists continue to exhibit low blood–brain-barrier penetration (e.g. brain/plasma [B/P] ratios < 1), poor oral bioavailability ($F\% < 20\%$), high volumes of distribution at steady state ($V_D > 10$ L/kg) and high plasma clearance ($Cl_{\text{plasma}} > 45$ ml/min/kg) [93]. However, several compounds exhibited more favorable overall pharmacokinetics. One compound from Neurocrine Biosciences was a potent ($K_i = 2$ nM), albeit rapidly cleared, imidazo[4,5-b]pyridin-2-one with good blood–brain-barrier penetration (B/P = 2.8; compound 16 g in Ref. [94]). Several from GlaxoSmithKline were less potent ($IC_{50} = 32$ –100 nM) substituted tetrahydropyrazolo[2,3-d]pyrimidines with excellent oral bioavailability (52–86%), balance between distribution and clearance and central accumulation (B/P = 2.3–3.7), including the clinical candidate GW876008 (see below) [95]. Two from Pfizer were potent ($K_i = 5$ –7 nM) 2-aryloxy-4-alkylaminopyridines, including the clinical candidate CP-316311 (see below) [96] and a successor with better solubility at stomach pH and food-independent oral bioavailability (compound 3a in Ref. [97]). An Eli Lilly and NIAAA collaboration yielded a highly potent ($K_i = 0.22$ nM) imidazo[1,2-b]pyridazine, with outstanding oral bioavailability (91%; 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine; MTIP) [55]. Finally, Bristol

Myers Squibb advanced two promising substituted pyrazolo[1,5-a]-1,3,5-triazines to clinical trials (BMS-561388 and their current lead candidate BMS-562086 [Pexacerfont], $IC_{50} = 6.1$ nM), which showed good pharmacokinetics in rat, dog and nonhuman primate models, no evidence of gastrointestinal or respiratory toxicity, and mild renal effects at doses approximately one order greater than those needed to substantially occupy brain CRF receptors [98]. Each of these compounds was active *in vivo* at minimum effective oral doses of 2–10 mg/kg in preclinical behavioral or endocrine animal models that are sensitive to CRF₁ signaling (Table 1).

Patent literature

As shown in Table 2, small-molecule CRF₁ antagonists disclosed recently in the patent literature (2006–2008) are also variations on the prevalent pharmacophore. Newer compounds have involved different cores, including heterocyclic pyrrolo[2,1-f]triazinones (e.g. WO 2008136377), benzimidazole derivatives (e.g. WO 2008082003, WO 2008051533 and WO 2006116412) and pyrazolo[4,3-d]pyrimidines (e.g. WO 2006126718), as well as monocyclic indanylamino-pyrazinopyridines (e.g. US 2006211710). In each of these variants, the proton-accepting nitrogen is present in the cycle adjacent to, rather than distal from, the 'down' aromatic (Table 2), which might allow for new substitution chemistries. Another development has been clear confirmation that the 'top' unit does not need to be branched alkyl chains (a feature that contributed to the undesirably high lipophilicity of the pharmacophore) but rather can tolerate polar, cyclic amines and related structures (e.g. WO2007039264, WO2006001501, WO2006001511, WO2006126718 and US2006211710). 'Down' units that are less lipophilic than the prototypical di- and tri-substituted phenyl aromatic are also now common antagonist features, including sulfur- and nitrogen-containing substituted rings (e.g. WO2008036579, WO2008036541, WO2006102194 and US2006211710).

Clinical development

Several CRF₁ antagonists from different pharmaceuticals have entered clinical trials since December 2004. Because an open-label Phase IIa trial showed that escalating doses of R121919 exhibited a good overall safety profile, normalized sleep electroencephalography and reduced depressive and anxious symptoms in depressed patients [6], clinical anticipation of CRF₁ antagonists has been high. However, R121919 development was discontinued because of isolated instances of elevated liver enzymes in a parallel trial. Despite major efforts (Table 3), no subsequent CRF₁ antagonist has successfully completed a definitive Phase III trial. By contrast, development of ONO-2333Ms and CP-316311 were discontinued because of negative efficacy results in double-blind, placebo-controlled trials for major depression [99]. Currently, the number of additional CRF₁ antagonists that are undergoing or have com-

TABLE 3

Selected recent patents for CRF₁ antagonists (2006–2008)

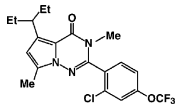
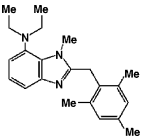
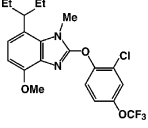
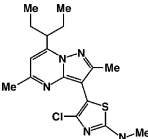
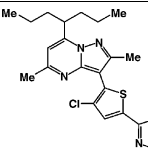
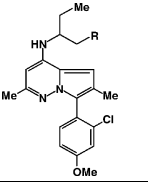
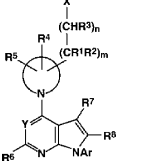
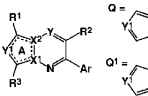
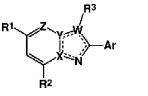
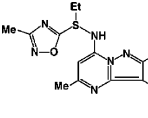
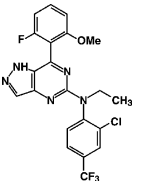
Compounds	Exemplar structure	Patent no.	Inventor(s)	Title	Notes
Pyrrolo[2,1-f][1,2,4] triazin-4(3H)-ones		WO 2008136377	Saito, Tetsuji; Obitsu, Tetsuo; Kagamiishi, Yoshifumi	Preparation of pyrrolo[2,1-f][1,2,4] triazin-4(3H)-ones as CRF antagonists	PCT Int. Appl. (2008), 237pp. CODEN: PIXXD2 WO 2008136377 A1 20081113 CAN 149:556672 AN 2008:1360515

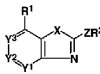
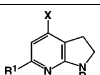
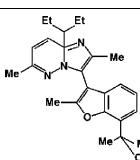
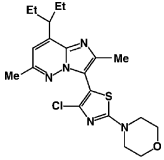
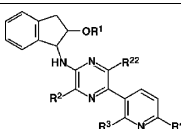
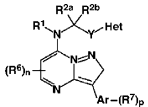
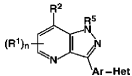
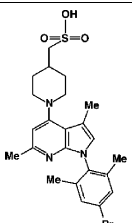
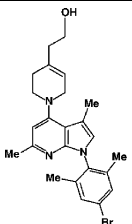
TABLE 3 (Continued)

Compounds	Exemplar structure	Patent no.	Inventor(s)	Title	Notes
Benzimidazole derivatives		WO 2008082003	Aso, Kazuyoshi; Mochizuki, Michiyo; Kobayashi, Katsumi	Benzimidazole derivatives as CRF receptor antagonists and their preparation, pharmaceutical compositions and use in the treatment of diseases	PCT Int. Appl. (2008), 77 pp. CODEN: PIXXD2 WO 2008082003 A1 20080710 CAN 149:128827 AN 2008:832827
Benzimidazole derivatives		WO 2008051533	Aso, Kazuyoshi; Mochizuki, Michiyo; Kojima, Takuto; Kobayashi, Katsumi; Pratt, Scott Alan; Gyorkos, Albert Charles; Corrette, Christopher Peter; Cho, Suk Young	Preparation of benzimidazole derivatives as CRF receptor antagonists	PCT Int. Appl. (2008), 216 pp. CODEN: PIXXD2 WO 2008051533 A2 20080502 CAN 148:517721 AN 2008:530180
Thiazolylpyrazolopyrimidines		WO 2008036579	Chen, Zhaogen; Hamdouchi, Chafiq Hamdouchi; Hembre, Erik James; Hipskind, Philip Arthur; Myers, Jason Kenneth; Takakuwa, Takako; Toth, James Lee	Thiazolylpyrazolopyrimidines as CRF1 receptor antagonists and their preparation, pharmaceutical compositions and use in the treatment of diseases	PCT Int. Appl. (2008), 60 pp. CODEN: PIXXD2 WO 2008036579 A1 20080327 CAN 148:379656 AN 2008:381087
Thiophene pyrazolopyrimidines		WO 2008036541	Chen, Zhaogen; Hamdouchi, Chafiq Hamdouchi; Hembre, Erik James; Hipskind, Philip Arthur; Jia, Shaojuan; Toth, James Lee	Preparation of thiophene pyrazolopyrimidine compounds as corticotropin releasing factor 1 (CRF1) receptor antagonists	PCT Int. Appl. (2008), 47 pp. CODEN: PIXXD2 WO 2008036541 A1 20080327 CAN 148:379655 AN 2008:380601
Pyrrolo[1,2-b]pyridazines		US 2007224636	Fu, Jian-Min	Pyrrolo [1,2b]pyridazine compound CRF receptor antagonists and their therapeutic use	U.S. Pat. Appl. Publ. (2007), 12 pp. CODEN: USXXCO US 2007224636 A1 20070927 CAN 147:378405 AN 2007:1088670
Pyrrolopyrimidines		JP 2007169216	Nakazato, Atsuro; Okubo, Takatoshi; Nozawa, Hiroshi; Minda, Tomoko; Kenneth, Ludo E.J.	Pharmaceuticals containing pyrrolopyrimidines for prophylactic or therapeutic treatment of corticotropin releasing factor (CRF)-associated diseases	Jpn. Kokai Tokkyo Koho (2007), 63 pp. CODEN: JKXXAF JP 2007169216 A 20070705 CAN 147:134454 AN 2007:726462
Pyrrolopyridazines		WO 2007069671	Nakai, Hisao; Saito, Tetsuji; Kagamiishi, Yoshifumi	Preparation of bicyclic heterocyclic compounds as antagonists of corticotropin releasing factor (CRF)	PCT Int. Appl. (2007), 60 pp. CODEN: PIXXD2 WO 2007069671 A1 20070621 CAN 147:72776 AN 2007:670590
Imidazo[1,2-a]pyridines Pyrrolo[1,5-a]pyridines Benzimidazole derivatives		WO 2007069565	Nakai, Hisao; Saito, Tetsuji; Kagamiishi, Yoshifumi	Preparation of bicyclic heterocyclic compounds as antagonists of corticotropin releasing factor (CRF)	PCT Int. Appl. (2007), 93 pp. CODEN: PIXXD2 WO 2007069565 A1 20070621 CAN 147:72759 AN 2007:670422
Pyrazolo[1,5-a]pyridines		WO 2007039264	Hossner, Frank	Pyrazolo[1,5-alpha]pyrimidiny] derivatives useful as corticotropin -releasing factor (CRF) receptor antagonists	PCT Int. Appl. (2007), 37 pp. CODEN: PIXXD2 WO 2007039264 A1 20070412 CAN 146:428737 AN 2007:409409
Pyrazolo[4,3-d]pyrimidines		WO 2006126718	Kashiwagi, Toshihiko; Takamuro, Iwao; Watanabe, Yumi; Yato, Michihisa	Preparation of pyrazolo[4,3-d]pyrimidine derivatives as CRF receptor antagonists	PCT Int. Appl. (2006), 94 pp. CODEN: PIXXD2 WO 2006126718 A1 20061130 CAN 146:27853 AN 2006:1252488

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TABLE 3 (Continued)

Compounds	Exemplar structure	Patent no.	Inventor(s)	Title	Notes
Benzimidazole derivatives		WO 2006116412	Gyorkos, Albert; Corrette, Christopher; Cho, Suk; Pratt, Scott; Siedem, Christopher; Aso, Kazuyoshi; Gyoten, Michiyo	Preparation of fused heterocyclic compounds like benzimidazoles as CRF receptor antagonists	PCT Int. Appl. (2006), 249 pp. CODEN: PIXXD2 WO 2006116412 A2 20061102 CAN 145:455015 AN 2006:1147073
Pyrrolopyridines		WO 2006108689	Andreotti, Daniele; Bacchi, Sergio; Delpogetto, Monica; Guelfi, Simone; Perboni, Alcide; Ribecai, Arianna; Spada, Simone; Stabile, Paolo; Tampieri, Marsia	Process for preparing heterocyclypyrrolopyridines and their use as antagonists of corticotropin-releasing factor (CRF) receptors	PCT Int. Appl. (2006), 42 pp. CODEN: PIXXD2 WO 2006108689 A2 20061019 CAN 145:438607 AN 2006:1093832
Imidazo[1,2b]pyridazines		WO 2006107784	Collins, Elizabeth Aaron; Garcia-Losada, Pablo; Hamdouchi, Chafiq; Hipskind, Philip Arthur; Lu, Jianliang; Takakuwa, Takako	Preparation of imidazo[1,2-b]pyridazine compounds as corticotropin releasing factor 1 receptor antagonists for treating psychiatric and neurological diseases	PCT Int. Appl. (2006), 171 pp. CODEN: PIXXD2 WO 2006107784 A1 20061012 CAN 145:419159 AN 2006:1066310
Imidazo[1,2b]pyridazines		WO 2006102194	Barbosa, Heather Janelle; Collins, Elizabeth Aaron; Hamdouchi, Chafiq; Hembre, Erik James; Hipskind, Philip Arthur; Johnston, Richard Duane; Lu, Jianliang; Rupp, Michael John; Takakuwa, Takako; Thompson, Richard Craig	Preparation of imidazo[1,2-b]pyridazine compounds as corticotropin releasing factor 1 receptor antagonists for treating psychiatric and neurol. Diseases	PCT Int. Appl. (2006), 205 pp. CODEN: PIXXD2 WO 2006102194 A1 20060928 CAN 145:356795 AN 2006:1006160
Indanylamino pyrazinylpyridines		US 2006211710	Verhoest, Patrick R.; Hoffmann, Robert L.	Preparation of indanylamino pyrazinylpyridines as corticotropin releasing factor CRF1 antagonists for treatment of CNS disorders	U.S. Pat. Appl. Publ. (2006), 11 pp. CODEN: USXXCO US 2006211710 A1 20060921 CAN 145:336081 AN 2006:980075
Pyrzolo[1,5a]pyrimidines		WO 2006044958	Lanier, Marion; Luo, Zhiyong; Moorjani, Manisha; Tellew, John Edward; Williams, John P.; Zhang, Xiaohu	Preparation of pyrrolo[1,5-a]pyrimidines as corticotropin releasing factor (CRF) receptor antagonists	PCT Int. Appl. (2006), 117 pp. CODEN: PIXXD2 WO 2006044958 A1 20060427 CAN 144:432830 AN 2006:382981
Pyrazolopyridines		WO 2006044821	Lanier, Marion; Moorjani, Manisha; Tellew, John Edward; Williams, John P.	Preparation of pyrazolopyridines as corticotropin releasing factor (CRF) receptor antagonists	PCT Int. Appl. (2006), 65 pp. CODEN: PIXXD2 WO 2006044821 A1 20060427 CAN 144:412502 AN 2006:382953
Pyrrolopyrimidines Pyrrolopyridines		WO 2006001511	Nakazato, Atsuro; Okubo, Taketoshi; Nozawa, Dai; Tamita, Tomoko; Kennis, Ludo E.J.	Preparation of pyrrolopyrimidine and pyrrolopyridine derivatives substituted with a cyclic amino group as CRF antagonists	PCT Int. Appl. (2006), 89 pp. CODEN: PIXXD2 WO 2006001511 A1 20060105 CAN 144:108345 AN 2006:13450
Pyrrolopyrimidines Pyrrolopyridines		WO 2006001501	Nakazato, Atsuro; Okubo, Taketoshi; Nozawa, Dai; Kennis, Ludo E.J.; De Bruyn, Marcel F.L.	Preparation of pyrrolopyrimidine and pyrrolopyridine derivatives substituted with tetrahydropyridine as CRF antagonists	PCT Int. Appl. (2006), 42 pp. CODEN: PIXXD2 WO 2006001501 A1 20060105 CAN 144:108344 AN 2006:13293

pleted undisclosed efficacy trials (Phase II/III) is at least three for major depression (GSK561679, GW876008 and Pexacerfont) and two for irritable bowel syndrome and social anxiety disorder (GSK561679 and GW876008). Several other candidates are earlier in the pipeline or their status has not been publicly updated by the pharmaceutical industry (e.g. GSK586529, TAI-041/JNJ19567470, SSR125543, NBI-34101 and antalarmin). Results from these trials should provide definitive conclusions regarding the therapeutic potential of CRF₁ antagonists for anxiety, depression and irritable bowel disorder and might pave the way for clinical evaluation in addictive disorders.

Disclosure statement

E.P.Z. and G.F.K. are inventors on a provisional patent filed for CRF₁ antagonists (application serial #9709/102,422). G.F.K.

currently provides consulting services to Alkermes, Boehringer-Ingelheim, Embera Pharmaceuticals, GlaxoSmithKline and Eli Lilly.

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