PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Docket No.: 103693.000585
Martine CLOZEL	Allowed: May 21, 2012
Appln. No.: 12/439,290	Group Art Unit: 1627
Patent No.: 8,268,847 B2	
Confirmation No.:	Examiner: CARTER, KENDRA D
Filed: February 27, 2009	Issued: September 18, 2012

For: THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

Mail Stop Supplemental Examination
Central Examination Unit
Commissioner for Patents
U.S. Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

REQUEST FOR SUPPLEMENTAL EXAMINATION

Pursuant to 37 U.S.C. § 257, Actelion Pharmaceuticals Ltd ("Patent Owner") requests supplemental examination of U.S. Patent No. 8,268,847 B2 ("the '847 patent"; Exhibit A). Actelion Pharmaceuticals Ltd is the owner of the '847 patent by virtue of the assignment that is recorded with the Patent and Trademark Office ("Office") at reel 028787, frame 0964.

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I. 37 C.F.R. § 1.610(a)

The required fee of $16,500 is submitted herewith, and includes the filing fee of $4,400 and the *ex parte* reexamination fee of $12,100. Patent Owner authorizes any charges or credits to Deposit Account No. 233050.

II. 37 C.F.R. § 1.610(b)(1)

Supplemental examination under 35 U.S.C. § 257 is requested for U.S. Patent No. 8,268,847 ("the '847 patent") entitled "THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR," which issued on September 18, 2012.

III. 37 C.F.R. § 1.610(b)(2)

The following are the items of information that are requested to be considered:

- U.S. Patent No. 7,094,781 ("the '781 patent")
- U.S. Patent No. 8,367,685 ("the '685 patent")
- WO 02/053557 ("the Bolli publication"; Exhibit B)
- WO 2006/026395 ("the Keyser publication"; Exhibit C)
- Office Action mailed February 28, 2012 during prosecution of the '847 patent (Exhibit D)

IV. 37 C.F.R. § 1.610(b)(3)

There are no other prior or concurrent post-grant proceedings involving the '847 patent.

V. 37 C.F.R. § 1.610(b)(4)

Supplemental examination is requested for claims 1-11 of the '847 patent (*i.e.* all of the claims of the patent).

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VI. 37 C.F.R. § 1.610(b)(5)

A. Summary of relevance

The above-noted items of information were cited as relevant to the claims of the '847 patent because they were cited in connection with rejections during the patent's prosecution.

During prosecution, the Examiner stated that the Bolli publication "constitutes prior art only under 35 U.S.C. 102(e)" (*see* Office Action mailed February 28, 2012, attached as Exhibit D, at page 8). The Examiner also stated that rejections based upon the publication could be overcome, *inter alia*, "by showing that the [publication] is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a)" (*id.* at pages 8-9).[1]

During prosecution, Applicant consistently presented substantive arguments traversing the Bolli publication and the other cited references on the merits. In response to the Examiner's statement, Applicant also confirmed that the subject matter of the Bolli publication and the claimed inventions were, at the time those inventions were made, owned by the same person or subject to an obligation of assignment to the same person (Reply filed April 27, 2012 to Office Action mailed February 28, 2012, at page 5). In the Notice of Allowance, the Examiner stated that the Bolli publication did not constitute prior art under 35 U.S.C. § 103(c) and withdrew all of the rejections (Notice of Allowance mailed May 21, 2012, at page 2).

The Bolli publication bears a publication date of July 11, 2002 (*see* Exhibit B). The patent application from which the '847 patent issued (*i.e.*, U.S. Patent Application No.

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[1] 35 U.S.C. § 103(c) provides that "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person."

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12/439,290) was filed on August 28, 2007, and claimed the benefit of two foreign priority applications, the earliest of which was filed August 29, 2006 (*see* Exhibit A). It appears, therefore, that the exchange between the Examiner and Applicant regarding 35 U.S.C. § 103(c) was not correct as a matter of law because the Bolli publication also constitutes § 102(b) art.[2]

In view of this error during prosecution, and because Patent Owner also maintains Applicant's substantive arguments traversing the Bolli publication and the other cited references on the merits, Patent Owner files this request for supplemental examination for consideration of the correction above.

B. The Examiner's manner of applying each item of information to the claims of the patent as stated in the Office Action mailed February 28, 2012

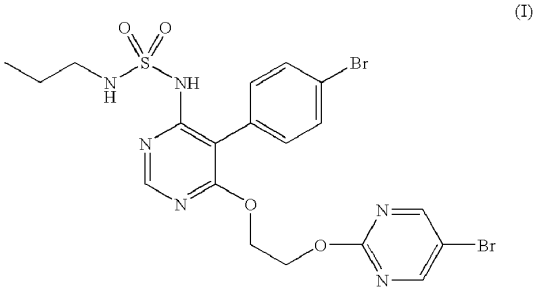
The above-noted items of information were cited as relevant for the reasons that the Examiner stated during prosecution of the '847 patent. The rejections and the manner of applying each item of information to the claims of the patent were stated in the Office Action mailed February 28, 2012, at pages 4-9 (*see* Exhibit D). A brief summary is as follows:

[2] There were no inaccuracies with regard to the facts of common ownership stated by Applicant.

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- **Rejection of claims 1-3 and 5-8 on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of the '781 patent in view of the Bolli publication and the Keyser publication**[3]

The '781 patent was said to teach the claimed compound, *i.e.*, the compound of Formula (I):



The Examiner acknowledged that the '781 patent did not teach the use of the compound with a PDE-5 inhibitor (*id.* at 4). The Examiner cited the Bolli publication as teaching use of the claimed compound as an ET antagonist (*id.*, citing page 28, first row, right compound of Exhibit B) and that the compound can be combined with an excipient and another active compound to treat conditions or diseases which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (*id.*, citing the Abstract and pages 16-17 of Exhibit B).

The Keyser publication was cited as teaching that ET antagonists and PDE-5 inhibitors may be combined together to treat cardiac disorders such as hypertension (*id.* at 5, citing the Abstract and claims 19 and 21 of Exhibit C). The Examiner then concluded that it would have been obvious to combine the claimed compound of Formula (I) and a PDE-5 inhibitor because the compound of Formula (I) is an ET antagonist and the Keyser publication teaches that ET antagonists and PDE-5 inhibitors can be combined to treat hypertension (*id.*).

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[3] The '781 patent is the U.S. national stage of PCT/EP01/14182, which corresponds to WO 02/053557, *i.e.*, the Bolli publication (Exhibit B).

- **Rejection of claims 1-3 and 5-8 provisionally on the ground of nonstatutory obviousness-type double patenting over claim 1 of copending Application No. 12/388,142 ("the '142 application"; later issued as the '685 patent) in view of the Bolli publication and the Keyser publication.[4]**

The reasons underlying this rejection parallel those set forth for the above-noted obviousness-type double patenting rejection over the '781 patent, except that the Examiner stated that the '142 application teaches the compound of Formula (I) (*id.* at 5-6).

- **Rejection of claims 1-3 and 5-8 under 35 U.S.C. §103(a) as being obvious over Bolli in view of Keyser.**

Similar to the obviousness-type double patenting rejections noted above, the Examiner cited the Bolli publication as teaching the claimed compound of Formula (I) as an ET antagonist (*id.* at 9, citing page 28, first row, right compound of Exhibit B) and that it can be combined with an excipient and another active compound to treat conditions or diseases which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (*id.*, citing the Abstract and pages 16-17 of Exhibit B). The Examiner acknowledged that the Bolli publication does not teach the claimed compound in combination with at least one compound having PDE-5 inhibitory properties, such as tadalafil (*id.* at 9).

The Examiner cited the Keyser publication as teaching that ET antagonists and PDE-5 inhibitors may be combined to treat cardiac disorders such as hypertension (*id.* at 9, citing the Abstract and claims 19 and 21 of Exhibit C). The Examiner concluded that it would be obvious to combine the claimed compound of Formula (I) and a PDE5 inhibitor because the claimed

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[4] Claims 1-3 and 5-8 were also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of co-pending Application No. 12/066,448 ("the '448 application") in view of the Bolli publication and the Keyser publication (*see* Exhibit D at pages 6-7). The '448 application, however, has been abandoned (*see* Notice of Abandonment mailed January 26, 2012).

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compound of Formula (I) is an ET antagonist and the Keyser publication teaches that ET antagonists and PDE-5 inhibitors may be combined to treat hypertension (*id.* at 9).

- **Claims 4 and 9-11**

During prosecution of the '847 patent, claims 4 and 9 were initially withdrawn from consideration due to a species election requirement, and claims 10-12 were initially withdrawn from consideration due to a restriction requirement (*see* Restriction Requirement mailed June 1, 2011, and Response to Restriction Requirement filed July 1, 2011). The Examiner's indication of allowable subject matter stated that claims 1-9 were allowable and, thus, included the remaining species encompassed by claims 4 and 9 (Notice of Allowance mailed May 21, 2012, at page 2). Given the allowability of claims 1-9, the Examiner rejoined claims 10 and 11 (claim 12 was canceled and its subject matter incorporated into claim 10) which were directed to methods for treating hypertension or pulmonary hypertension by administering "an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE-5-inhibitory properties, in free or pharmaceutically acceptable salt form" (*see id.*). Claims 10-12 were said to be free of the art (*id.* at 3). Accordingly, the relevance and manner of applying each item of information to claims 4 and 9-11 was the same as that for claims 1-3 and 5-8.

The above-noted manner in which the Examiner applied each item of information to the claims is also set forth in a claim chart attached as Appendix 1.

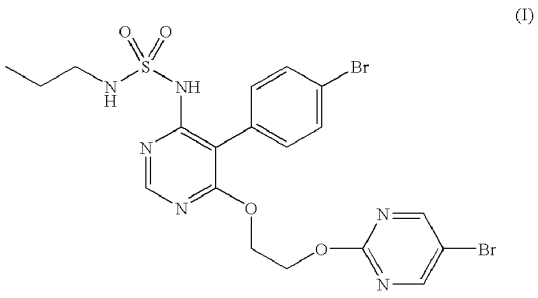
VII. 37 C.F.R. § 1.610(c)

Although the Bolli publication was incorrectly found to not qualify as prior art during prosecution of the '847 patent, Patent Owner submits that the items of information listed above do not raise a substantial new question of patentability with respect to the '847 patent's claims.

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Patent Owner submits that patentability of these claims exists for the same reasons that similar claims in two continuation patent applications, *i.e.*, Application No. 13/604,148 ("the '148 application") and Application No. 14/162,280 ("the '280 application"), were allowed on a prosecution record where the status of the references as prior art was maintained throughout the prosecution.[5]

During prosecution of the '148 application, the Patent Trial and Appeal Board ("Board") considered the items of information identified herein in relation to claims directed to methods of treating hypertension, pulmonary hypertension or pulmonary arterial hypertension comprising administering simultaneously, separately, or over a period of time, to a patient in need thereof, an effective amount of a compound of Formula (I):



in free or pharmaceutically acceptable salt form, and at least one compound having PDE-5-inhibitory properties, in free or pharmaceutically acceptable salt form. *See Ex parte Clozel*, Appeal 2014-009320 (Oct. 3, 2016) ("Decision"; attached as Exhibit E).[6]

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[5] A terminal disclaimer over the '847 patent has been filed in the '148 application (*see* Terminal Disclaimer filed December 5, 2016).

[6] The Decision is addressed in connection with 37 C.F.R. §1.610(c), and a copy is provided for convenience.

The Board considered rejections of claims 1-14 for: (1) obviousness under 35 U.S.C. § 103(a) over the Bolli publication in view of the Keyser publication; (2) non-statutory obviousness-type double patenting over claims 8 and 9 of the '781 patent in view of the Bolli publication and the Keyser publication; and (3) non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of the '142 application (later issued as the '685 patent) in view of the Bolli publication and the Keyser publication (Exhibit E at page 3).

The Board reversed all of these rejections (*id.*).[7] In doing so, the Board found, *inter alia*, that the Examiner did not adequately respond to Applicant's argument that the claimed inventions produce unexpectedly superior results (*id.*).

The Board also found that Applicant presented persuasive evidence that an ordinarily skilled artisan would not have expected the synergistic effects produced by the administration of the compound of Formula (I) and a PDE-5 inhibitor (*id.* at 9). For example, the Board noted that the compound of Formula (I) is a dual ET_A-ET_B (*i.e.*, nonselective) inhibitor, and the Keyser publication teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects" (*id.* at 9, citing Exhibit C at ¶ 67).

Specifically, the Keyser publication was said to teach that ET_A causes vasoconstriction such that the administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension (*id.* at 9, citing Exhibit C at ¶ 68). The Board further

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[7] Similar rejections presented in the '280 application were withdrawn by the Examiner in view of the Board Decision in the '148 application (*see* Office Action mailed December 29, 2016, at page 2).

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noted that ET_B, on the other hand, was said to cause vasodilation wherein ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP (cyclic guanosine monophosphate) levels (*id.* at 10, citing Exhibit C at ¶ 68). The Board noted that the Keyser publication further discloses that cGMP relaxes blood vessels, but PDE-5 breaks down cGMP (*id.*). The Keyser publication also discloses that administration of a PDE-5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE-5 antagonist (*id.*). Conversely, the Keyser publication explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production" (*id.*).

Based on this description, the Board found that an ordinarily skilled artisan would not have expected the administration of a nonselective ET antagonist, such as the compound of Formula (I), and a PDE-5 antagonist to produce the synergistic results reported in Applicant's specification (*id.*). In fact, the Board stated that "[i]f anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser" (*id.*, citing Exhibit C at ¶¶68-69). For these reasons, the Board reversed the rejections of claims 1-14 for obviousness over the Bolli publication in view of the Keyser publication due to lack of supporting evidence (*id.*).

For the same reasons, the Board also reversed the rejections of claims 1-14 for non-statutory obviousness-type double patenting based on the '781 patent and the '142 application (later issued as the '685 patent) (*id.* at 11).

For at least the reasons that the Board identified in reversing the then-pending rejections in the '148 application, Patent Owner submits that the above-noted items of information do not raise a substantial new question of patentability as to the claims of the '847 patent.

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VIII. Conclusion

In view of the above, Patent Owner respectfully submits this request for supplemental examination of claims 1-11 of the '847 patent and that a supplemental examination certificate be issued.

Respectfully submitted,

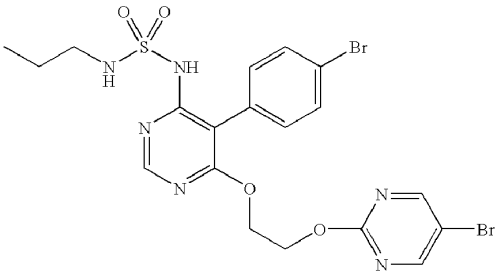
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APPENDIX 1

Claims of U.S. Patent No. 8,268,847	**Examiner's manner of applying each item of information to the claims of the patent**
1. A product containing the compound of formula (I) below  (I) in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.	**'781 patent:** Examiner states it teaches the claimed compound and notes that it does not teach the composition with a PDE-5 inhibitor such as tadalafil. (*See, e.g.*, **Exhibit D** at page 4) **'142 application (later issued as the '685 patent):** Examiner states it teaches a composition of the claimed compound and notes it does not teach a combination with a PDE-5 inhibitor such as tadalafil. (*See, e.g.*, **Exhibit D** at page 5) **Bolli publication:** Examiner states it teaches the claimed compound as an ET antagonist (citing page 28, first row, right compound) in compositions that can be combined with an excipient and another active compound to treat conditions or diseases which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (citing Abstract; pages 16-17) and notes that it does not teach a combination with at least one compound having PDE-5 inhibitory properties such as tadalafil. (*See, e.g.*, **Exhibit D** at pages 4, 6, 9) **Keyser publication:** Examiner states it teaches that ET antagonists and PDE-5 inhibitors such as tadalafil may be combined together to treat cardiac disorders such as hypertension (citing Abstract and claims 19 and 21). (*See, e.g.*, **Exhibit D** at pages 5, 6, 9)
2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication

3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
5. The product according to claim 1, wherein the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
6. A pharmaceutical composition containing, as active principles, the compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form, as well as at least one excipient.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication

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10. A method for the treatment of hypertension or pulmonary hypertension comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication
11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.	See citations associated with claim 1, including particularly the Examiner's citation of the Abstract and claims 19 and 21 of Keyser publication

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EXHIBIT A

US008268847B2

(12) **United States Patent**
Clozel

(10) **Patent No.: US 8,268,847 B2**
(45) **Date of Patent: Sep. 18, 2012**

(54) **THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR**

(75) Inventor: **Martine Clozel**, Binningen (CH)

(73) Assignee: **Actelion Pharmaceuticals, Ltd.**, Allschwil (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 599 days.

(21) Appl. No.: **12/439,290**

(22) PCT Filed: **Aug. 28, 2007**

(86) PCT No.: **PCT/IB2007/053448**

§ 371 (c)(1),
(2), (4) Date: **Feb. 27, 2009**

(87) PCT Pub. No.: **WO2008/026156**

PCT Pub. Date: **Mar. 6, 2008**

(65) **Prior Publication Data**

US 2009/0318459 A1 Dec. 24, 2009

(30) **Foreign Application Priority Data**

Aug. 29, 2006 (WO) PCT/IB2006/052999
Oct. 19, 2006 (WO) PCT/IB2006/053857

(51) **Int. Cl.**
A01N 43/54 (2006.01)
A61K 31/505 (2006.01)
C07D 401/00 (2006.01)

(52) **U.S. Cl.** **514/269**; 546/274.4

(58) **Field of Classification Search** 514/269; 546/274.4

See application file for complete search history.

(56) **References Cited**

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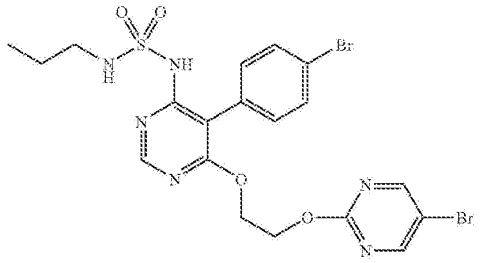
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Primary Examiner — Sreeni Padmanabhan
Assistant Examiner — Kendra D Carter
(74) *Attorney, Agent, or Firm* — Hoxie & Associates LLC

(57) **ABSTRACT**

The invention relates to a product containing the compound of formula (I) below

(I)



or a pharmaceutically acceptable salt of this compound, in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

11 Claims, No Drawings

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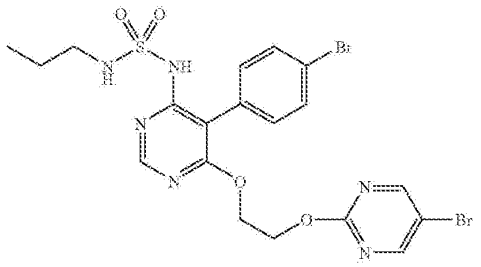
THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a United States National Stage Application under 35 U.S.C. 371 of PCT Application No. PCT/IB2007/053448, filed on Aug. 28, 2007, which claims the benefit of PCT Application No. PCT/IB2006/052999, filed on Aug. 29, 2006, and PCT Application No. PCT/IB2006/053857, filed on Oct. 19, 2006, the contents of each of which are incorporated herein by reference in their entirety.

The present invention relates to a product containing the compound of formula (I) below

(I)



or a pharmaceutically acceptable salt of this compound, in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

PCT publication WO 02/053557 describes endothelin receptor antagonists including the compound of formula (I) and the use of said endothelin receptor antagonists in the treatment of various diseases wherein vasoconstriction is involved (i.a. heart failure, angina pectoris, pulmonary and systemic hypertension and erectile dysfunction).

PDE-5 inhibitors have been notably described in the following patent documents:

- U.S. Pat. No. 5,250,534 (describing pyrazolopyrimidinone derivatives as PDE-5 inhibitors and i.a. sildenafil as well as the use of the same for i.a. hypertension and heart failure) and EP 1097 711 (describing i.a. sildenafil for pulmonary hypertension);
- WO 99/24433 (describing i.a. vardenafil as well as the use of the same for i.a. hypertension, angina pectoris and erectile dysfunction);
- U.S. Pat. No. 5,859,006 (describing i.a. tadalafil as well as the use of the same for i.a. hypertension, pulmonary hypertension, angina and congestive heart failure);
- WO 00/27848 (describing i.a. udenafil and the use thereof for impotence).

The Applicant has now surprisingly found that the combination of the compound of formula (I) with a compound having PDE5-inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved.

Therefore a subject of this invention is a product containing the compound of formula (I) as described before or a pharmaceutically acceptable salt of said compound of formula (I),

in combination with at least one (and preferably one) compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

The following paragraphs provide definitions of the various terms used in the present patent application and are intended to apply uniformly throughout the specification and claims, unless an otherwise expressly set out definition provides a broader or narrower definition.

"PDE-5" stands in the present application for cyclic guanosine 3', 5'-monophosphate (cGMP) phosphodiesterase type 5.

"Simultaneously" or "simultaneous", when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients by the same route and at the same time.

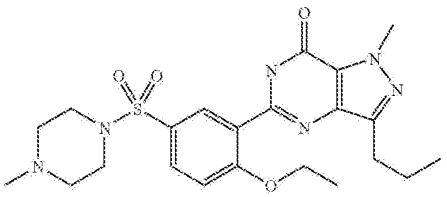
"Separately" or "separate", when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

By therapeutic administration "over a period of time" is meant in the present application the administration of two or more ingredients at different times, and in particular an administration method according to which the entire administration of one of the active ingredients is completed before the administration of the other or others begins. In this way it is possible to administer one of the active ingredients for several months before administering the other active ingredient or ingredients. In this case, no simultaneous administration occurs.

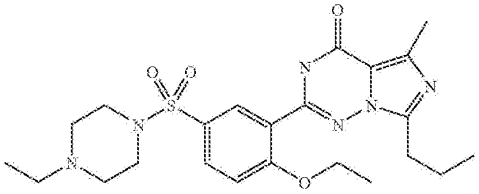
By "disease wherein vasoconstriction is involved" is meant in particular hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.

By "compound having PDE5-inhibitory properties" is meant a compound that, when submitted to the "Test for the determination of PDE5 IC_{50}" described in the present patent application, has an IC_{50} equal or lower than 1 μM.

Specific examples of compounds having PDE5-inhibitory properties include the compounds having the following structures (names):

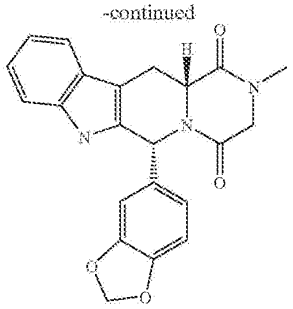


(sildenafil)

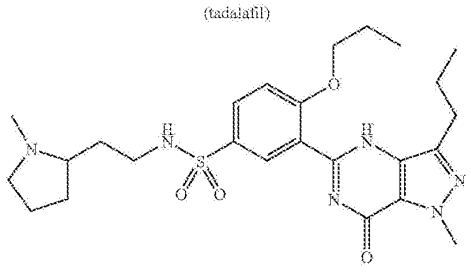


(vardenafil)

-continued



(tadalafil)



(udenafil)

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts. Reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), 33, 201-217.

Besides, any reference to a compound of formula (I) or to a compound having PDE5-inhibitory properties is to be understood as referring also to the pharmaceutically acceptable salts thereof, as appropriate and expedient.

Preferably, the product according to this invention will be such that the compound of formula (I) and the compound having PDE5-inhibitory properties are intended for a therapeutic use which takes place simultaneously or over a period of time.

According to one preferred variant of this invention, the compound of formula (I) and the compound having PDE5-inhibitory properties will be intended to be administered simultaneously.

According to another preferred variant of this invention, the compound of formula (I) and the compound having PDE5-inhibitory properties will be intended to be administered over a period of time.

The period of time intended for the therapeutic use of a product according to this invention will be at least one week, and preferably at least one or more months (for example six months). This period of time may also be the whole life of the patient that receives the product. Preferably, administration of compound of formula (I) will be alternated with administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days (and more preferably not exceed one day).

Preferably, the compound having PDE5-inhibitory properties will be selected from sildenafil, vardenafil, tadalafil and udenafil. More preferably, the compound having PDE5-inhibitory properties will be sildenafil or tadalafil.

According to one particularly preferred variant of the invention the compound having PDE5-inhibitory properties will be sildenafil.

According to another particularly preferred variant of the invention the compound having PDE5-inhibitory properties will be tadalafil.

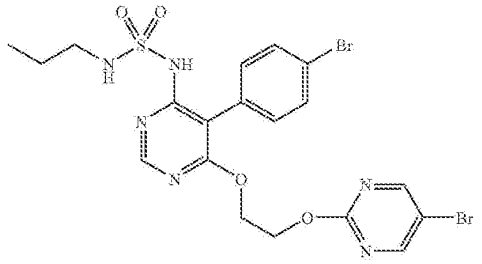
The administration route of the compound of formula (I) and that of the compound having PDE5-inhibitory properties is preferably the same. In particular, the common administration route for the compound of formula (I) and for the compound having PDE5-inhibitory properties will be the intravenous or oral route (and notably the oral route).

Though the exact administration doses of a product according to this invention will have to be determined by the treating physician, it is expected that a dose of 0.05 to 2 mg (and preferably 0.1 to 1 mg) of compound of formula (I) per kg of patient body weight combined with a dose 0.01 to 1 mg (and preferably 0.05 to 0.5 mg) of tadalafil per kg of patient body weight, both compounds being intended to be administered by oral route, or combined with a dose 0.1 to 2 mg (and preferably 0.2 to 1 mg) of sildenafil per kg of patient body weight will be appropriate, both compounds being intended to be administered by oral route as well.

Preferably, the disease intended to be treated by a product according to this invention will be selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris. More preferably, the disease intended to be treated by a product according to this invention will be selected from hypertension and pulmonary hypertension. In particular, the disease intended to be treated by a product according to this invention will be pulmonary hypertension (and notably pulmonary arterial hypertension).

The invention also relates to a pharmaceutical composition containing, as active principles, the compound of formula (I) below

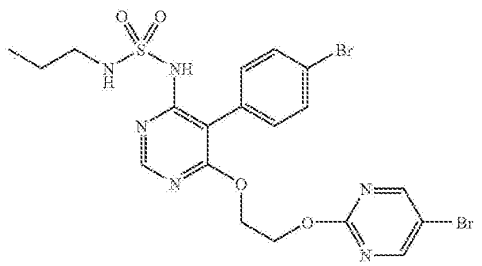
(I)



or a pharmaceutically acceptable salt of this compound, in combination with at least one (and preferably one) compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, as well as at least one excipient.

The invention further relates to the use of the compound of formula (I) below

(I)



or a pharmaceutically acceptable salt of this compound, in combination with at least one (and preferably one) compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament intended to treat a disease wherein vasodilation is required.

Besides, preferences indicated for the product according to this invention of course apply mutatis mutandis to the pharmaceutical compositions and uses of this invention.

Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

EXAMPLES

To illustrate the usefulness of this invention, the association of the compound of formula (I), administered orally at a dose of 0.3 mg/kg, with tadalafil, administered orally at a dose of 10 mg/kg, has been studied in two different hypertension models, namely the Dahl salt-sensitive rat model and the spontaneously hypertensive rat model. Furthermore, the association of the compound of formula (I), administered orally at a dose of 0.3 mg/kg, with sildenafil, administered orally at a dose of 30 mg/kg, has been studied in the spontaneously hypertensive rat model. The protocols used are detailed in the part entitled "Pharmacological properties of the invention compounds" hereafter.

Pharmacological Properties of the Invention Compounds

The experimental methods described hereafter can be used to show the pharmacological properties of the invention compounds.

Dahl Salt-Sensitive Rat Model

Dahl salt-sensitive (Dahl-S) were purchased from Harlan (Netherlands). The rats were housed by group during the acclimatization period and single-housed after implantation of the telemetry device. All animals were maintained under identical conditions and had free access to normal pelleted rat chow and water. Dahl salt-sensitive rats develop hypertension only upon exposure to salt intake. They were administered a high-salt (8%) chow diet (Purina series 5500). Five weeks after starting salt administration, a telemetry system was implanted under anaesthesia by inhalation of 2.5% isoflurane (in 70% O_2+30% N_2O). Under aseptic conditions, a pressure radio-frequency transmitter was implanted into the peritoneal cavity, and a sensing catheter was inserted in the descending aorta and advanced pointing upstream to slightly below the renal artery bifurcation. The transmitter was sutured to the abdominal musculature and the skin was closed. A receiver platform transformed the radio signal into digitized input, that was sent to a dedicated personal computer (Compaq, deskpro). Arterial blood pressure measurements were calibrated by using an input from an ambient pressure reference. Telemetry units were obtained from Data Sciences (St. Paul, Minn., USA).

The compounds were administered at least 2 weeks after telemetry system implantation. The compound of formula (I) and the compound having PDE5-inhibitory properties were prepared in 5% arabic gum and administered by oral gavage. The acute effects of the compound of formula (I), the compound having PDE5-inhibitory properties and their combination on blood pressure were measured by collecting data at 5-minute intervals up to 72 h after oral administration. Hourly means of blood pressure were calculated for each rat. Each rat served as its own control, by using the blood pressure data of the last 24 hours before drug administration. The two curves (blood pressure of the control period and blood pressure of the treatment period) were plotted together and the area between curves (ABC) from 0 to 72 hours was calculated. The higher the ABC, the stronger the effect of the item tested for lowering blood pressure.

Spontaneously Hypertensive Rat Model

The same protocol was used as for the Dahl salt-sensitive rat model, except that spontaneously hypertensive rats (SHR) replace the Dahl-S rats and that the SHR rats did not receive any salt diet. The SHR rats were purchased from Harlan (Netherlands).

Test for the Determination of PDE5 IC_{50}:

In order to estimate the extent of inhibition for PDE5 activity of a test compound, the following test is carried out. Phosphodiesterase-5 enzyme (PDE 5) is separated from human corpus cavernosal tissues. About 3 g of this tissue is homogenized with 12 ml of HEPES buffer (20 mM HEPES, 250 mM sucrose, 1 mM EDTA, 1 mM PMSF, pH 7.2) at 4° C. The solution is filtered with double-layered gauze and centrifuged (100.000×g) for 60 min at 4° C. The supernatant is filtered with 0.2 μm filter paper and separated by HPLC (Mono Q anion exchange column) with concentration gradient of 0-500 mM NaCl to elute PDE isozymes. The enzyme activity is measured on each column fraction by the following process to separate the PDE5 fraction and the PDE5 inhibition of the test compound is measured using the PDE5 fraction. To 1.5 ml tube are added 100 μl of reaction mixture (15 mM Tris-HCl, 5 mM $MgCl_2$, 0.5 mg/ml BSA, pH 7.4) and the appropriate amount of test compound fraction and test compound and the mixture is mixed well. To this solution is added ^{3}H-cAMP or ^{3}H-cGMP (500 nM, 2 μCi/ml), the mixture is reacted in the incubator of 30° C. for about 1 hour and the reaction is quenched by putting the tube into boiling water for about 45 seconds to 2 min. Then the tube is chilled in ice bath for about 5 min. To this tube is added snake venom (1 mg/ml, 100 μl) or 5-nucleotidase (0.1 unit/tube) and the mixture is reacted in an incubator at 37° C. for 10 min and chilled in an ice bath. 3 times volume of methanol to the resin is added to the anion exchange resin (Bio-Rad resin. AG 1-X2, 200-400 mesh) which has been already washed with 0.5N HCl, H_2O, 0.5N NaOH, H_2O, 0.5N MCl and H_2O in order and adjusted to pH 5. Then 1 ml of the pretreated resin is dispensed into each tube with vortexing. The mixture is left at 4° C. for 15 min with occasional vortexing and centrifuged (10,000 rpm) for about 5 min to sediment the resin. The supernatant (700 μl) is transferred to a liquid scintillation vial, and mixed with 10 ml of scintillation cocktail. After stabilizing the solution by leaving it overnight, the radioactivity of the tube is measured by β-counter.

If the test compound has an IC_{50} equal or lower than 1 μM, it is considered as having PDE5-inhibitory properties for the purpose of this patent application. If the test compound has an IC_{50} higher than 1 μM, it is considered as not having PDE5-inhibitory properties for the purpose of this patent application.

Example 1

Following the test protocol described previously in the part entitled "Dahl salt-sensitive rat model", oral administration of the compound of formula (I) and tadalafil decreased blood pressure in Dahl-S rats: the compound of formula (I) (0.3 mg/kg) decreased blood pressure with an ABC of 256 and tadalafil (10 mg/kg) with an ABC of 310. The ABC after oral administration of the combination (compound of formula (I) at 0.3 mg/kg and tadalafil at 10 mg/kg) was 923, demonstrating a synergistic effect.

Example 2

Following the test protocol described previously in the part entitled "Spontaneously hypertensive rat model", oral admin-

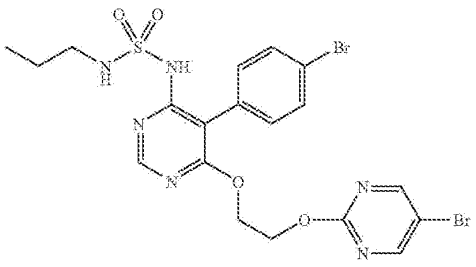
istration of the compound of formula (I) and tadalafil decreased blood pressure in SHR rats: the compound of formula (I) (0.3 mg/kg) decreased blood pressure with an ABC of 44 and tadalafil (10 mg/kg) with an ABC of 286. The ABC after oral gavage of the combination (compound of formula (I) at 0.3 mg/kg and tadalafil at 10 mg/kg) was 444, confirming the synergistic effect.

Example 3

Following the test protocol described previously in the part entitled "Spontaneously hypertensive rat model", oral administration of the compound of formula (I) and sildenafil decreased blood pressure in SHR rats: the compound of formula (I) (0.3 mg/kg) decreased blood pressure with an ABC of 38 and sildenafil (30 mg/kg) with an ABC of 229. The ABC after oral gavage of the combination (compound of formula (I) at 0.3 mg/kg and sildenafil at 30 mg/kg) was 317, confirming the synergistic effect.

The invention claimed is:

1. A product containing the compound of formula (I) below



(I)

in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

2. The product according to claim **1**, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

3. The product according to claim **2**, wherein the compound having PDE5-inhibitory properties is tadalafil.

4. The product according to claim **2**, wherein the compound having PDE5-inhibitory properties is sildenafil.

5. The product according to claim **1**, wherein the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.

6. A pharmaceutical composition containing, as active principles, the compound of formula (I) as described in claim **1**, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form, as well as at least one excipient.

7. The pharmaceutical composition according to claim **6**, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim **7**, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim **7**, wherein the compound having PDE5-inhibitory properties is sildenafil.

10. A method for the treatment of hypertension or pulmonary hypertension comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim **1**, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

11. The method according to claim **10**, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

* * * * *

EXHIBIT B

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WO 02/053557 A1

(54) Title: NOVEL SULFAMIDES AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to novel sulfamides of general formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as endothelin receptor antagonists.

NOVEL SULFAMIDES AND THEIR USE AS ENDOTHELIN RECEPTOR ANTAGONISTS

The present invention relates to novel pyrimidine-sulfamides of the general formula I and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general formula I and especially their use as endothelin receptor antagonists.

Endothelins (ET-1, ET-2, and ET-3) are 21-amino acid peptides produced and active in almost all tissues (Yanagisawa M et al.: Nature (1988) **332**:411). Endothelins are potent vasoconstrictors and important mediators of cardiac, renal, endocrine and immune functions (McMillen MA et al.: J Am Coll Surg (1995) **180**:621). They participate in bronchoconstriction and regulate neurotransmitter release, activation of inflammatory cells, fibrosis, cell proliferation and cell differentiation (Rubanyi GM et al.: Pharmacol Rev (1994) **46**:328).

Two endothelin receptors have been cloned and characterized in mammals (ET_A, ET_B) (Arai H et al.: Nature (1990) **348**:730; Sakurai T et al.: Nature (1990) **348**:732). The ET_A receptor is characterized by higher affinity for ET-1 and ET-2 than for ET-3. It is predominant in vascular smooth muscle cells and mediates vasoconstricting and proliferative responses (Ohlstein EH et al.: Drug Dev Res (1993) **29**:108). In contrast, the ET_B receptor has equivalent affinity for the three endothelin isopeptides and binds the linear form of endothelin, tetra-ala-endothelin, and sarafotoxin S6C (Ogawa Y et al.: BBRC (1991) **178**:248). This receptor is located in the vascular endothelium and smooth muscles, and is also particularly abundant in lung and brain. The ET_B receptor from endothelial cells mediates transient vasodilator responses to ET-1 and ET-3 through the release of nitric oxide and/or prostacyclin whereas the ET_B receptor from smooth muscle cells exerts vasoconstricting actions (Sumner MJ et al.: Brit J Pharmacol (1992)

107:858). ET_A and ET_B receptors are highly similar in structure and belong to the superfamily of G-protein coupled receptors.

A pathophysiological role has been suggested for ET-1 in view of its increased plasma and tissue levels in several disease states such as hypertension, pulmonary hypertension, sepsis, atherosclerosis, acute myocardial infarction, congestive heart failure, renal failure, migraine and asthma. As a consequence, endothelin receptor antagonists have been studied extensively as potential therapeutic agents. Endothelin receptor antagonists have demonstrated preclinical and/or clinical efficacy in various diseases such as cerebral vasospasm following subarachnoid hemorrhage, heart failure, pulmonary and systemic hypertension, neurogenic inflammation, renal failure and myocardial infarction.

Today, only one endothelin receptor antagonist (Tracleer™) is marketed and several are in clinical trials. However, some of these molecules possess a number of weaknesses such as complex synthesis, low solubility, high molecular weight, poor pharmacokinetics, or safety problems (e.g. liver enzyme increases). Furthermore, the contribution of differing ET_A / ET_B receptor blockade to the clinical outcome is not known. Thus, tailoring of the physicochemical and pharmacokinetic properties and the selectivity profile of each antagonist for a given clinical indication is mandatory. So far, no endothelin receptor antagonists with a pyrimidine core structure containing a sulfamide unit, have been reported [2, 3, 5, 6, 8]. We have discovered a new class of substituted pyrimidines of the structure below and found that they allow the specific tailoring described above and in addition compounds exhibiting mixed as well as ET_A-selective binding profiles have been identified.

The inhibitory activity of the compounds of general formula I on endothelin receptors can be demonstrated using the test procedures described hereinafter:

For the evaluation of the potency and efficacy of the compounds of the general formula I the following tests were used:

1) Inhibition of endothelin binding to membranes from CHO cells carrying human ET receptors:

For competition binding studies, membranes of CHO cells expressing human recombinant ET_A or ET_B receptors were used. Microsomal membranes from recombinant CHO cells were prepared and the binding assay made as previously described (Breu V., et al, FEBS Lett 1993; **334**:210).

The assay was performed in 200 uL 50 mM Tris/HCl buffer, pH 7.4, including 25 mM $MnCl_2$, 1 mM EDTA and 0.5% (w/v) BSA in polypropylene microtiter plates. Membranes containing 0.5 ug protein were incubated for 2 h at 20°C with 8 pM [^{125}I]ET-1 (4000 cpm) and increasing concentrations of unlabelled antagonists. Maximum and minimum binding were estimated in samples without and with 100 nM ET-1, respectively. After 2 h, the membranes were filtered on filterplates containing GF/C filters (Unifilterplates from Canberra Packard S.A. Zürich, Switzerland). To each well, 50 uL of scintillation cocktail was added (MicroScint 20, Canberra Packard S.A. Zürich, Switzerland) and the filter plates counted in a microplate counter (TopCount, Canberra Packard S.A. Zürich, Switzerland).

All the test compounds were dissolved, diluted and added in DMSO. The assay was run in the presence of 2.5% DMSO which was found not to interfere significantly with the binding. IC_{50} was calculated as the concentration of antagonist inhibiting 50 % of the specific binding of ET-1. For reference compounds, the following IC_{50} values were found: *ET_A cells*: 0.075 nM (n=8) for ET-1 and 118 nM (n=8) for ET-3; *ET_B cells*: 0.067 nM (n=8) for ET-1 and 0.092 nM (n=3) for ET-3.

The IC_{50} values obtained with compounds of general formula I are given in Table 1.

Table 1:

Compound of Example	IC_{50}[nM] ET_A	ET_B
Example 1	721	8429
Example 2	2190	8743
Example 3	1384	744
Example 4	96	680
Example 5	28	1280
Example 6	286	7240
Example 7	1237	9467
Example 8	1160	>10000
Example 9	3629	>10000
Example 10	2866	193
Example 12	59	>10000
Example 14	5.6	1033
Example 15	18.5	2161
Example 16	45	8452
Example 18	8.5	3333
Example 19	25	3414
Example 20	4.9	1723
Example 21	7	1001
Example 22	12	434
Example 23	3.6	1585
Example 24	2.2	2496
Example 26	54	>10000
Example 29	13.5	4230

Example 32	3.5	864
Example 33	3.7	609
Example 34	23	3267
Example 37	16	822
Example 38	14.5	290
Example 39	32.7	524
Example 41	3.2	41.6
Example 42	3.5	146
Example 43	6.8	214
Example 48	1.46	46.6
Example 49	0.82	25.4
Example 50	0.87	7.5
Example 51	13.4	306
Example 55	5.2	80
Example 56	6.9	164
Example 57	4.9	35.8
Example 59	5.6	124
Example 60	3.4	232
Example 61	1.6	200
Example 66	11	487
Example 71	23.6	635
Example 73	1.9	567
Example 74	1.8	164
Example 75	14	895
Example 80	10	>1000
Example 81	3.6	274
Example 84	37	574

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Example 88	16	1251
Example 89	19	621
Example 90	7.4	433
Example 91	2.5	79
Example 96	6.3	585
Example 97	1.55	92
Example 98	2.1	159
Example 100	0.76	283
Example 101	1.24	335
Example 102	0.46	65
Example 104	0.88	601
Example 105	0.69	203
Example 107	0.25	96
Example 108	0.28	56
Example 109	1.94	>1000
Example 110	2.3	>1000
Example 111	12.3	3750
Example 112	0.52	257
Example 113	4.26	581
Example 114	8.3	>1000
Example 115	2.2	>1000
Example 116	1.3	567
Example 117	0.45	518
Example 118	0.34	611
Example 119	4.2	>1000
Example 123	2.9	124
Example 124	7.3	102
Example 127	7.3	87

Example 130	3.7	347
Example 131	3.2	233
Example 133	1.7	212
Example 134	2.4	187
Example 137	2.7	173
Example 138	0.9	40
Example 142	2.6	108
Example 143	3.1	35
Example 145	1.64	>1000
Example 146	5	514
Example 147	1.2	408
Example 149	15	1315
Example 151	0.77	57
Example 152	1.1	79
Example 155	5.8	173
Example 156	18	409
Example 157	42.2	954
Example 158	10	80
Example 160	11	3221
Example 161	6.2	>1000
Example 163	0.44	80
Example 164	1	81
Example 166	1	3
Example 167	5.2	6.4
Example 168	2.7	1.6
Example 170	1.7	42
Example 171	11	61
Example 172	3	16
Example 174	3.7	93

Example 175	22	62
Example 176	2.5	22
Example 181	14.3	224
Example 182	29	1867
Example 184	29.5	3777
Example 187	9.8	532
Example 188	11	290
Example 193	3.6	>1000
Example 194	9.5	>1000
Example 196	4.4	>1000
Example 197	1.16	418
Example 198	38.4	667
Example 199	12	205
Example 200	23	310
Example 201	133	682
Example 202	9.6	351
Example 204	390	1047
Example 205	135	623
Example 206	1.03	209
Example 207	17	>1000
Example 208	17	342
Example 209	733	>1000
Example 210	23	936
Example 211	290	722
Example 212	3.1	>1000
Example 213	1.32	347
Example 214	0.76	241

2) Inhibition of endothelin-induced contractions on isolated rat aortic rings (ET_A receptors) and rat tracheal rings (ET_B receptors):

The functional inhibitory potency of the endothelin antagonists was assessed by their inhibition of the contraction induced by endothelin-1 on rat aortic rings (ET_A receptors) and of the contraction induced by sarafotoxin S6c on rat tracheal rings (ET_B receptors). Adult Wistar rats were anesthetized and exsanguinated. The thoracic aorta or trachea were excised, dissected and cut in 3-5 mm rings. The endothelium/epithelium was removed by gentle rubbing of the intimal surface. Each ring was suspended in a 10 ml isolated organ bath filled with Krebs-Henseleit solution (in mM; NaCl 115, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5, glucose 10) kept at 37°C and gassed with 95% O_2 and 5% CO_2. The rings were connected to force transducers and isometric tension was recorded (EMKA Technologies SA, Paris, France). The rings were stretched to a resting tension of 3 g (aorta) or 2 g (trachea). Cumulative doses of ET-1 (aorta) or sarafotoxin S6c (trachea) were added after a 10 min incubation with the test compound or its vehicle. The functional inhibitory potency of the test compound was assessed by calculating the concentration ratio, i.e. the shift to the right of the EC_{50} induced by different concentrations of test compound. EC_{50} is the concentration of endothelin needed to get a half-maximal contraction, pA_2 is the negative logarithm of the antagonist concentration which induces a two-fold shift in the EC_{50} value.

The pA_2 values obtained with compounds of formula I are given in Table 2.

Table 2:

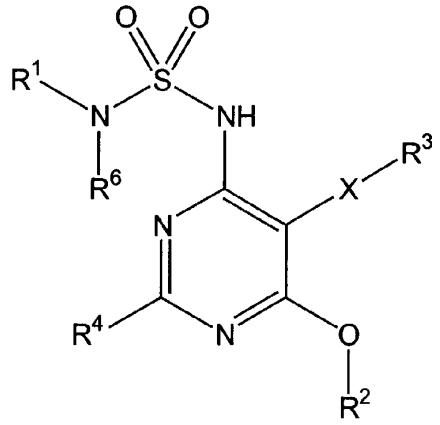
Compound of Example	pA_2 value	
	ET_A	ET_B
Example 5	6.65	
Example 14	8.4	5.63
Example 18	8.15	< 5
Example 20	7.21	
Example 32	8.75	
Example 37	7.83	
Example 41	8.37	
Example 51	6.55	
Example 100	8.44	
Example 102	8.40	6.76
Example 119	7.38	
Example 133	7.72	
Example 161	6.29	
Example 203	7.69	5.84

Because of their ability to inhibit the endothelin binding, the described compounds can be used for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, pulmonary hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome and portal hypertension. They can also be used in the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases, presently known to be related to endothelin.

The compounds can be administered orally, rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol. Examples of applications are capsules, tablets, orally administered suspensions or solutions, suppositories, injections, eye-drops, ointments or aerosols/nebulizers.

Preferred applications are intravenous, intra-muscular, or oral administrations as well as eye drops. The dosage used depends upon the type of the specific active ingredient, the age and the requirements of the patient and the kind of application. Generally, dosages of 0.1 – 50 mg / kg body weight per day are considered. The preparations with compounds can contain inert or as well pharmacodynamically active excipients. Tablets or granules, for example, could contain a number of binding agents, filling excipients, carrier substances or diluents.

The present invention relates to pyrimidine-sulfamides of the **general formula I**,



General Formula I

wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; hydrogen or may form a heterocyclyl- or cycloalkyl-ring together with R^6;

R^2 represents $-CH_3$; $-(CH_2)_n-Y-R^a$; $-(CH_2)_m-C\equiv C-(CH_2)_p-Z-R^a$; $-(CH_2)_k-C(R^b)=CR^cR^d$; $-CH_2$-tetrahydrofuran-2-yl;

R^3 represents aryl; heteroaryl;

R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N-(lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy; heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-

lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; cycloalkyl-sulfinyl;

R^6 represents hydrogen; lower alkyl; or may form a heterocyclyl- or cycloalkyl-ring together with R^1;

X represents oxygen; sulfur; $-CH_2-$ or a bond;

Y represents a bond, -O-; -NH-; $-NH-SO_2-$; $-NH-SO_2-NH-$; O-CO-; -CO-O-; -O-CO-NH-; -NH-CO-O-; -NH-CO-NH-

Z represents oxygen or a bond;

k represents the whole numbers 1, 2, 3, 4, 5 or 6;

n represents the whole numbers 2, 3, 4, 5 or 6;

m represents the whole numbers 1, 2, 3, 4 or 5;

p represents the whole numbers 0 (zero), 1, 2 or 3 and if p represents the whole number 0 (zero), Z cannot represent oxygen;

R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; hydrogen;

R^b and R^c independently represent hydrogen or lower alkyl;

R^d represents represents hydrogen; lower alkyl; aryl; heteroaryl;

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

In the definitions of the general formula I – if not otherwise stated – the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms. Examples of lower alkyl and lower alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.- butyl, tert.-butyl, pentyl, hexyl, heptyl, methoxy, ethoxy, propoxy, butoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. Lower alkylendioxy-groups are preferably methylen-dioxy and ethylen-dioxy groups. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g.vinylen, propenylen and butenylen. Lower alkenyl and lower alkynyl means groups like ethenyl, propenyl, butenyl, 2-methyl-propenyl, and ethinyl, propinyl, butinyl, pentinyl, 2-methyl-pentinyl. Lower alkenyloxy means allyloxy, vinyloxy and propenyloxy. The expression ***cycloalkyl*** means a saturated cyclic hydrocarbon ring with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which may be substituted with lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, and lower alkoxy-lower alkyl groups. The expression ***heterocyclyl*** means saturated or unsaturated (but not aromatic), four, five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings may be adequatly substituted with lower alkyl, lower alkoxy, e.g. piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, dihydroimidazolyl, dihydropyrazolyl, pyrazolidinyl and substituted derivatives of such rings with substituents as outlined above. The expression ***heteroaryl*** means six-membered aromatic rings containing one to four nitrogen atoms, benzofused six-membered aromatic rings containing one to three nitrogen atoms, five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, benzo- fused five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, five membered aromatic rings containig an oxygen and nitrogen atom and benzo fused derivatives thereof, five

membred aromatic rings containing a sulfur and a nitrogen atom and benzo fused derivatives thereof, five- membered aromatic rings containing two nitrogen atoms and benzo fused derivatives thereof, five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; e.g. furanyl, thienyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, oxazolyl, isoxazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, 5-thioxo-1,2,4-oxadiazolyl, 2-oxo-1,2,3,5-oxathiadiazolyl, whereby such rings may be substituted with lower alkyl, lower alkenyl, amino, amino-lower alkyl, halogen, hydroxy, lower alkoxy, trifluoromethoxy, trifluoromethyl, carboxyl, carboxamidyl, thioamidyl, amidinyl, lower alkoxy-carbonyl, cyano, hydroxy-lower alkyl, lower alkyl-oxy-lower alkyl or another heteroaryl- or heterocyclyl-ring. The expression ***aryl*** represents unsubstituted as well as mono-, di- or tri-substituted aromatic rings with 6 to 10 carbon atoms like phenyl or naphthyl rings which may be substituted with aryl, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkenyloxy, lower alkynyl-lower alkyl-oxy, lower alkenylen, lower alkylenoxy or lower alkylendioxy forming with the phenyl ring a five- or six-membered ring, hydroxy-lower alkyl, hydroxy-lower alkenyl, hydroxy-lower alkyl-lower alkynyl, lower alkyloxy-lower alkyl, lower alkyloxy-lower alkyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyl, hydroxy-cycloalkyl, heterocyclyl, heteroaryl.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p- toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula I might have one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and also in the meso-form. The present invention encompasses all these forms. Mixtures may be separated in a

manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

Because of their ability to inhibit the endothelin binding, the described compounds of the general formula I and their pharmaceutically acceptable salts may be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, coronary diseases, cardiac insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, portal hypertension and pulmonary hypertension. They can also be used for the treatment or prevention of atherosclerosis, restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, hyperlipidemia as well as other diseases presently known to be related to endothelin.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered intramuscularly, parenterally or intraveneously, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols may be used. For the preparation of solutions and sirups e.g. water, polyols,

saccharose, glucose can be used. Injectables can be prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin or liposomes. Suppositories may be prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols.

The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer or anti-oxidants.

The compounds of general formula I may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol and the like; vasodilators like hydralazine, minoxidil, diazoxide or flosequinan; calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil or nifedipine; ACE-inhibitors like cilazapril, captopril, enalapril, lisinopril and the like; potassium activators like pinacidil; angiotensin II receptor antagonists like losartan, valsartan, irbesartan and the like; diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone or chlortalidone; sympatholitics like methyldopa, clonidine, guanabenz or reserpine and other therapeutics which serve to treat high blood pressure or any cardiac disorders.

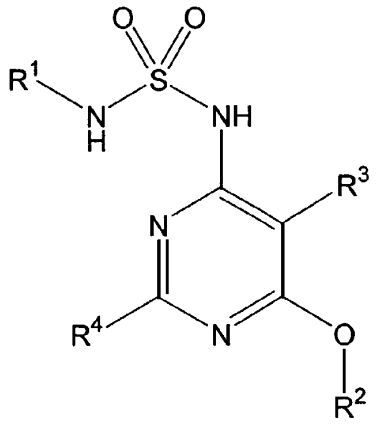
The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual children should receive lower doses which are adapted to body weight and age.

Preferred compounds are compounds of general formula I wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkyloxy, especially methoxy and **X** represents oxygen and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

A second group of preferred compounds of general formula I are those wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy, especially methoxy, **X** represents oxygen and R^2 represents $-(CH_2)_n$-Y-R^a and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

A third group of preferred compounds of general formula I are those wherein R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy, especially methoxy, **X** represents oxygen and R^2 represents $-(CH_2)_2$-O-R^a, with R^a being heteroaryl and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

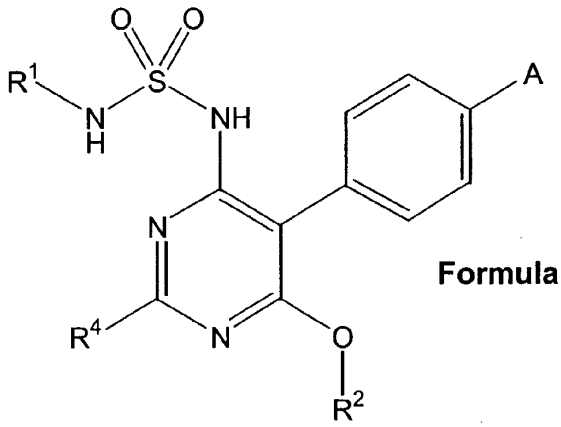
Another group of preferred compounds are compounds of **formula II**



Formula II

wherein R^1, R^2, R^3 and R^4 are as defined in general formula I above and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula II.

Also preferred are compounds of **formula III**

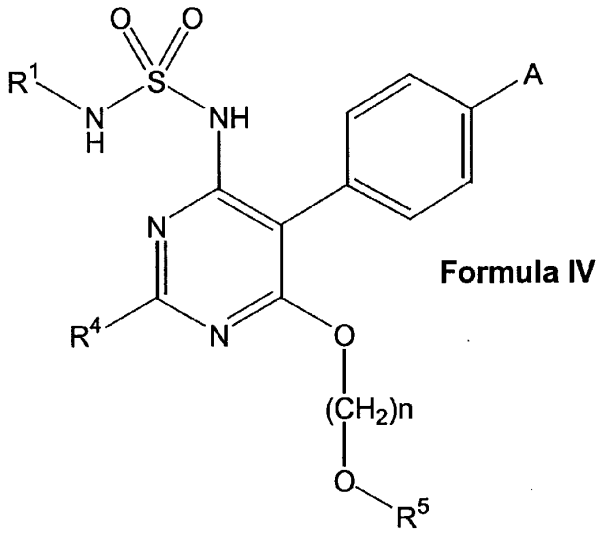


Formula III

wherein R^1, R^2 and R^4 are as defined in general formula I above and **A** represents hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy and optically pure enantiomers or diastereomers, mixtures of enantiomers or

diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula III.

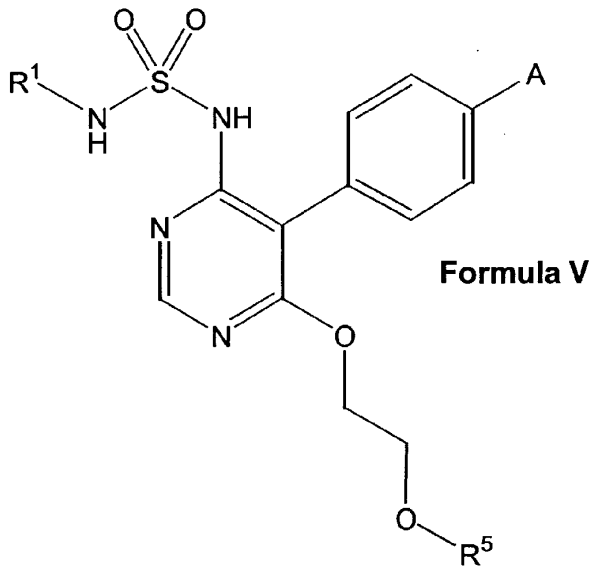
Also preferred are compounds of **formula IV**



Formula IV

wherein R^1, R^4 and **n** are as defined in general formula I above and **A** is as defined in formula III above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

Another especially preferred group of compounds are compounds of **formula V**



Formula V

wherein R^1 is as defined in general formula I above, **A** is as defined in formula III above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

Especially preferred compounds among the group of compounds of formula V are those wherein R^5 represents heteroaryl and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

Preferred compounds are:

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(4-methoxy-benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Benzylsulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid-[5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-Bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-2-pyridin-4-yl-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-2-pyridin-4-yl-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

More preferred compounds are:

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

2-Pyridylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

2-Thienylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

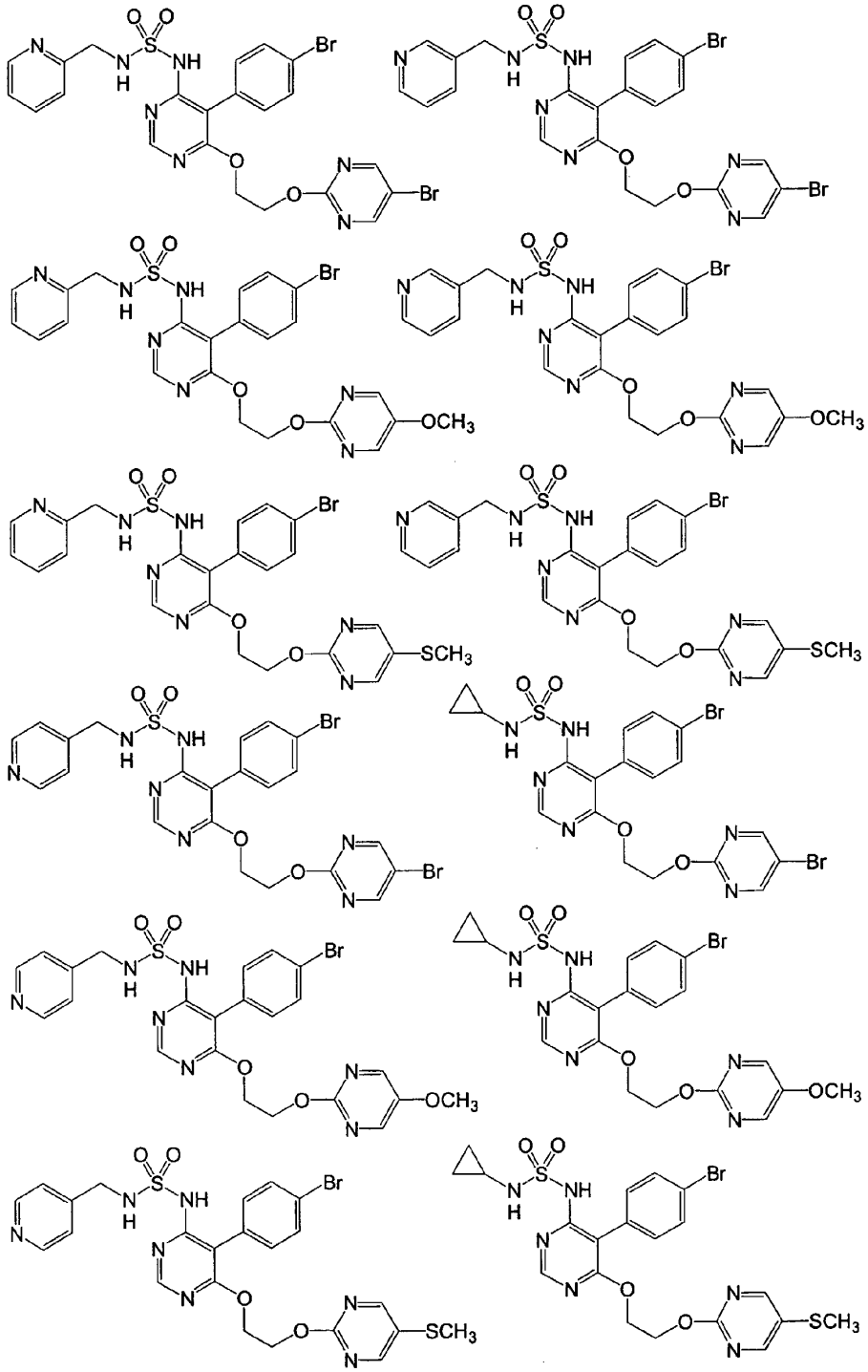
Most preferred compounds are:

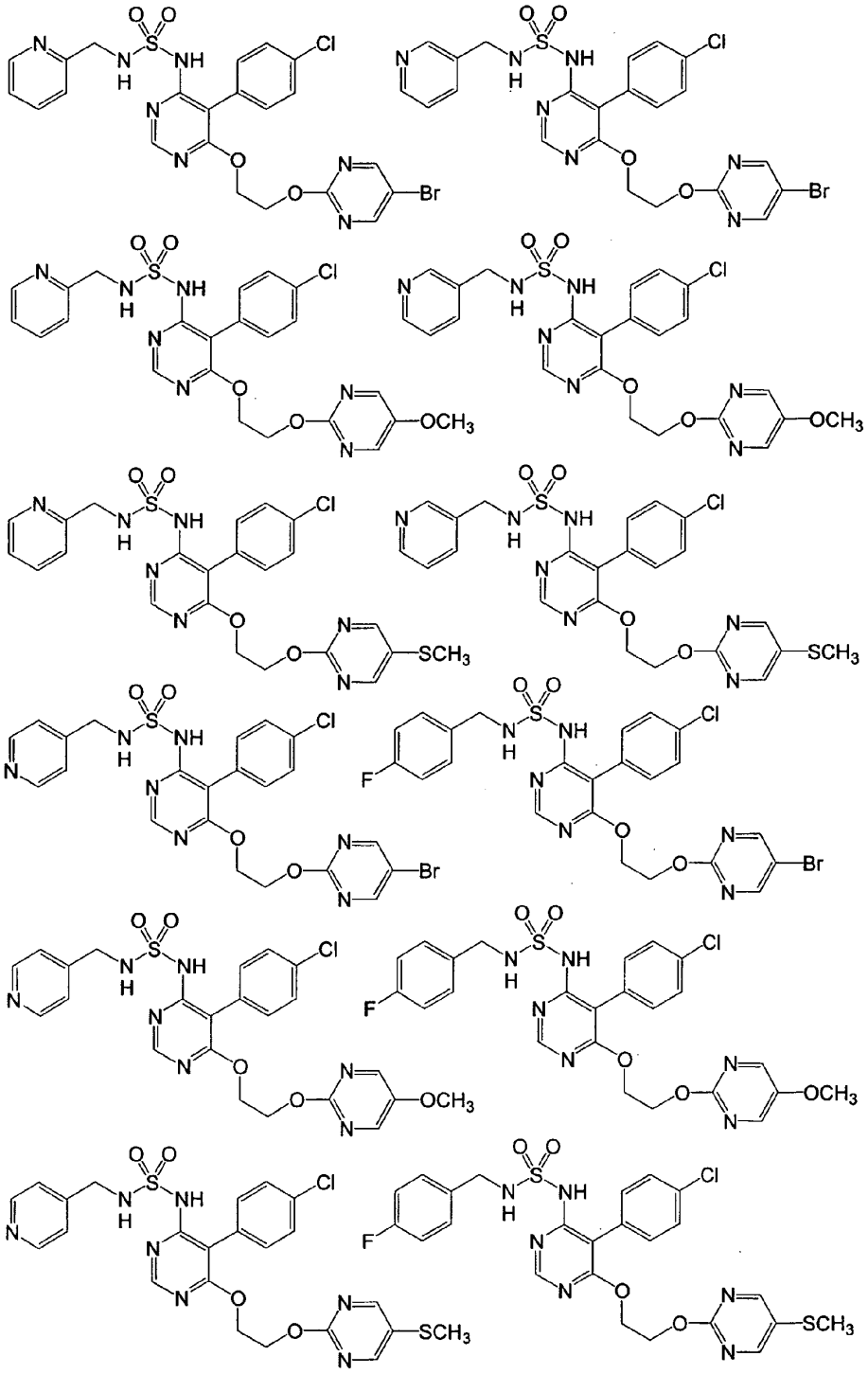
Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

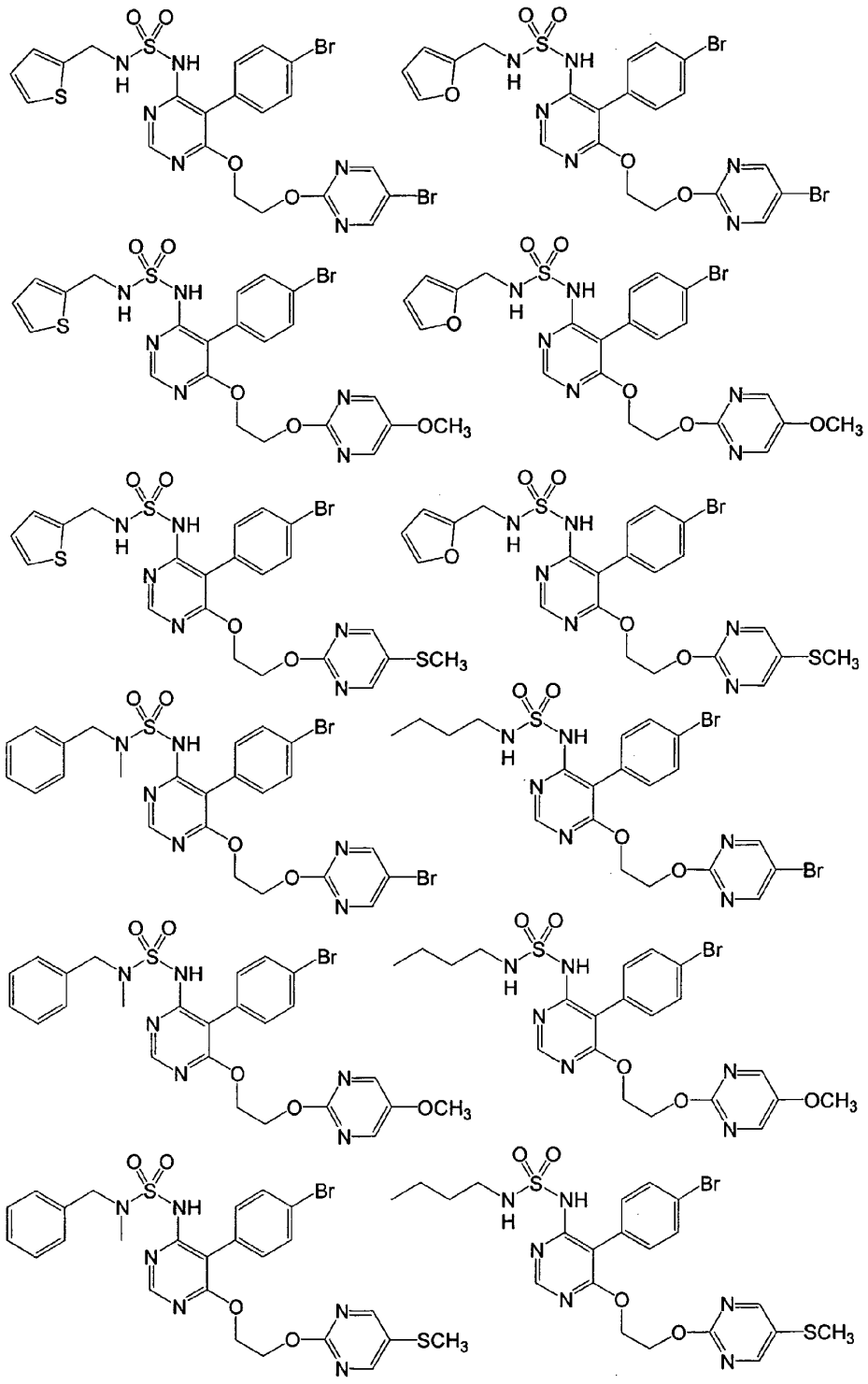
Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

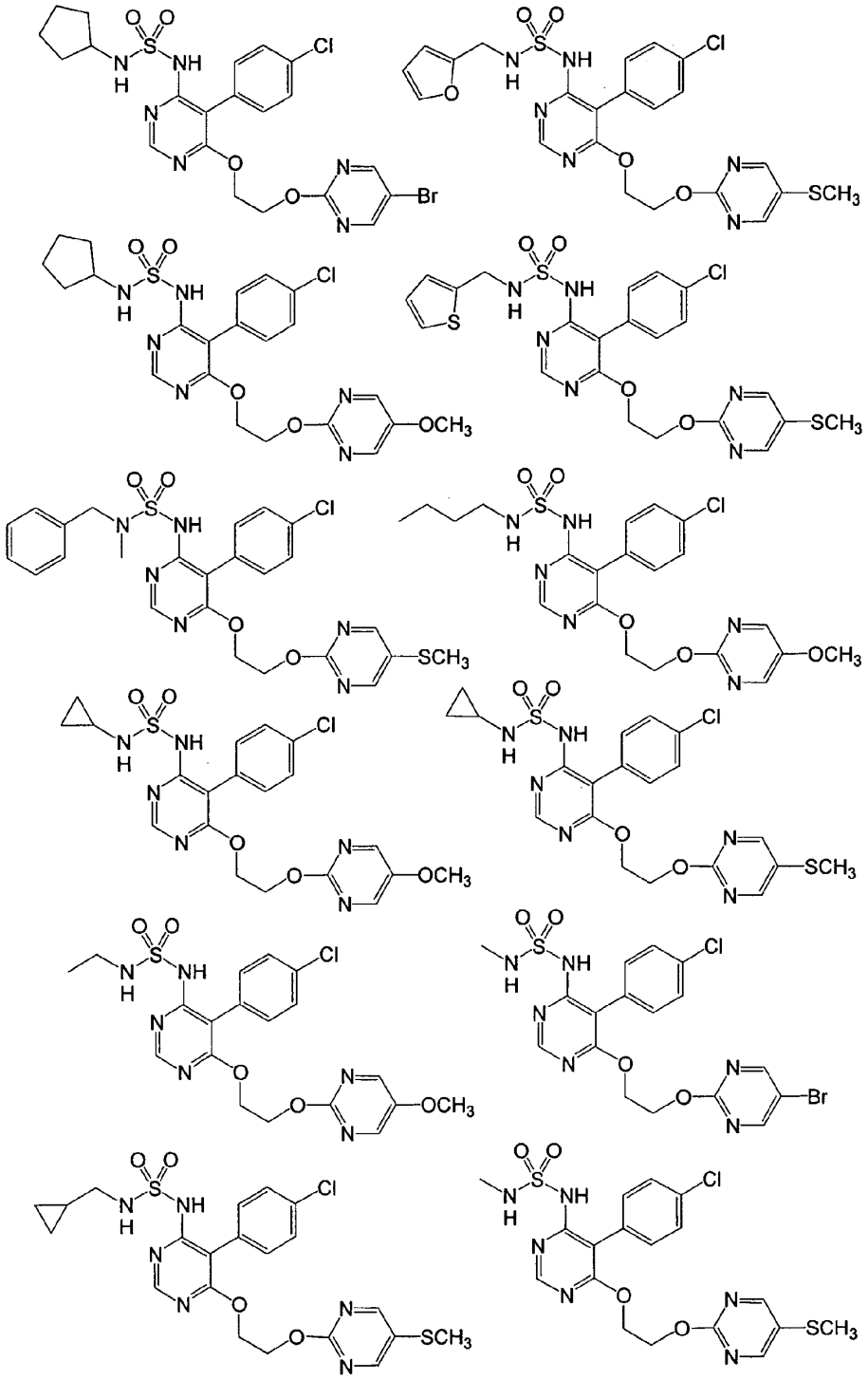
and pharmaceutically acceptable salts thereof.

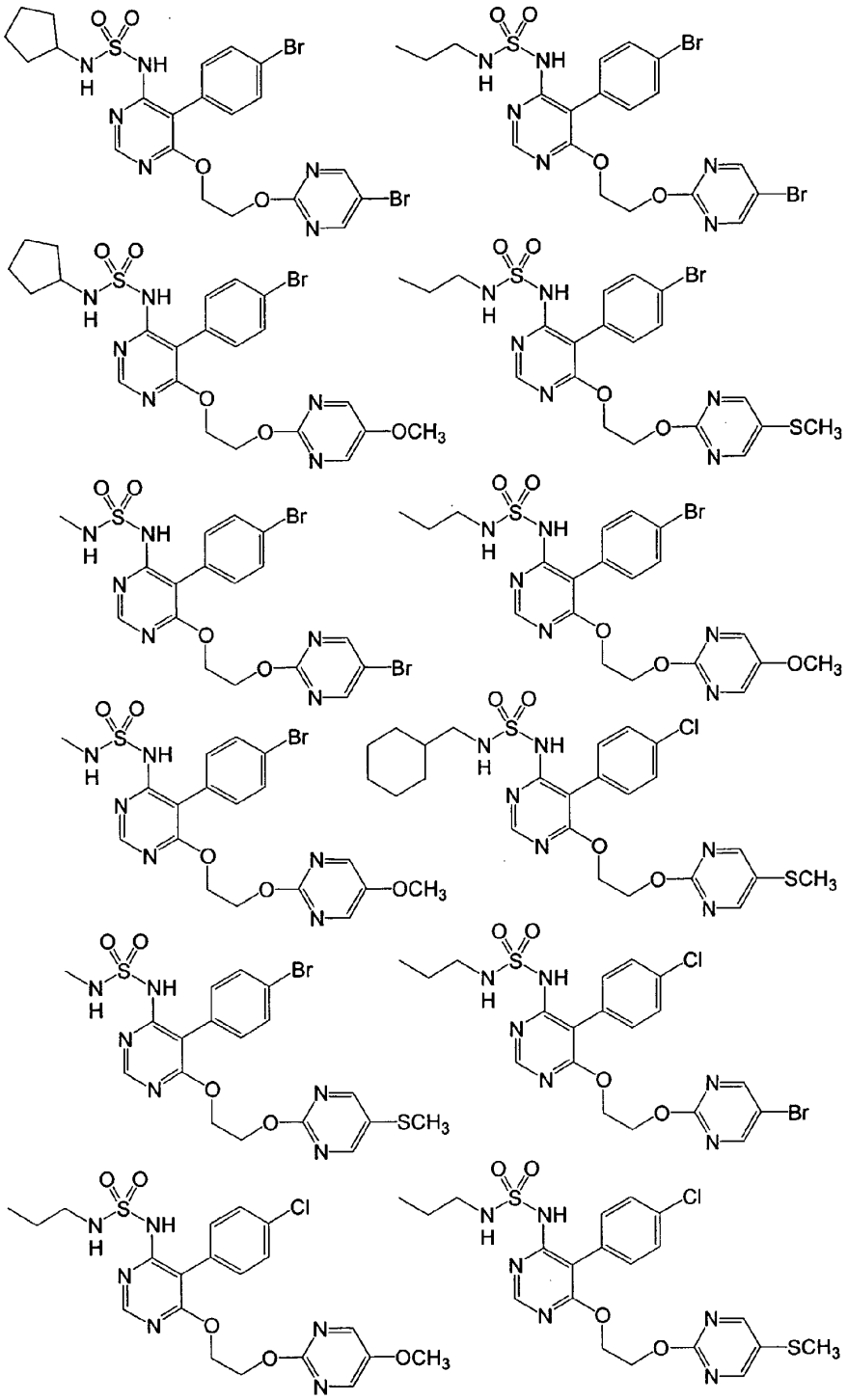
Another group of preferred compounds is depicted below:







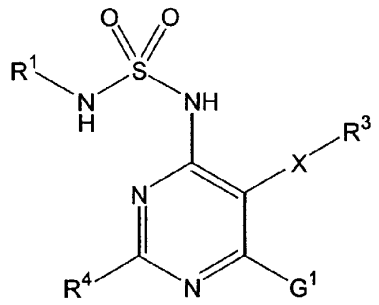




Compounds of the **general formula I** of the present invention can be prepared according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only parts of the synthetic possibilities which lead to compounds of general formula I are described. The literature references given in brackets [ ] are set forth at the end of this paragraph.

Possibility A:

The desired compounds of general formula I can be prepared by reacting a compound of the formula **1**:



Formula 1

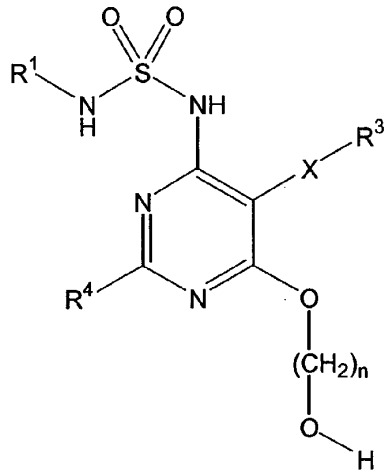
wherein G^1 is a reactive residue, preferentially a chloro atom, and the other symbols are as defined in general formula I above, with a compound of the formula **2**:

R^2—OH **Formula 2**

wherein the symbols are the same as defined in general formula I above, or a salt thereof.

Possibility B:

The compounds of general formula I may also be prepared by reacting a compound of formula **3**:



Formula 3

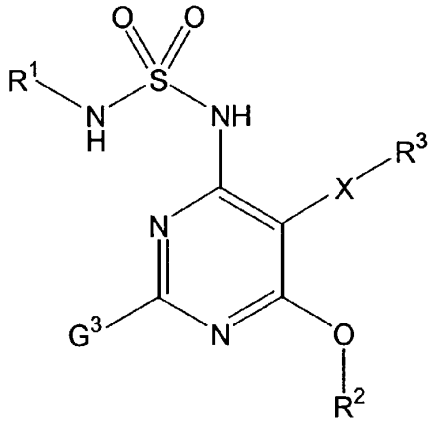
wherein the symbols are the same as defined in general formula I above, or a salt thereof, with a compound of the formula **4**:

G^2—R^5 **Formula 4**

wherein G^2 is a reactive residue, preferentially a halogen atom, and R^5 is the same as defined in formula IV above.

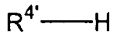
Possibility C:

The compounds of general formula I may also be prepared by reacting a compound of the formula **5**:



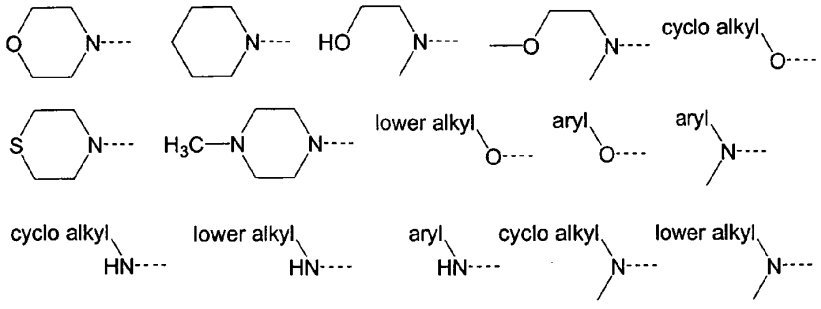
Formula 5

Wherein G^3 is a lower alkylsulfonyl group or a phenylsulfonylgroup or a halogen atom, and the other symbols are the same as described in general formula I above, or a salt thereof, with a compound of the formula **6**:



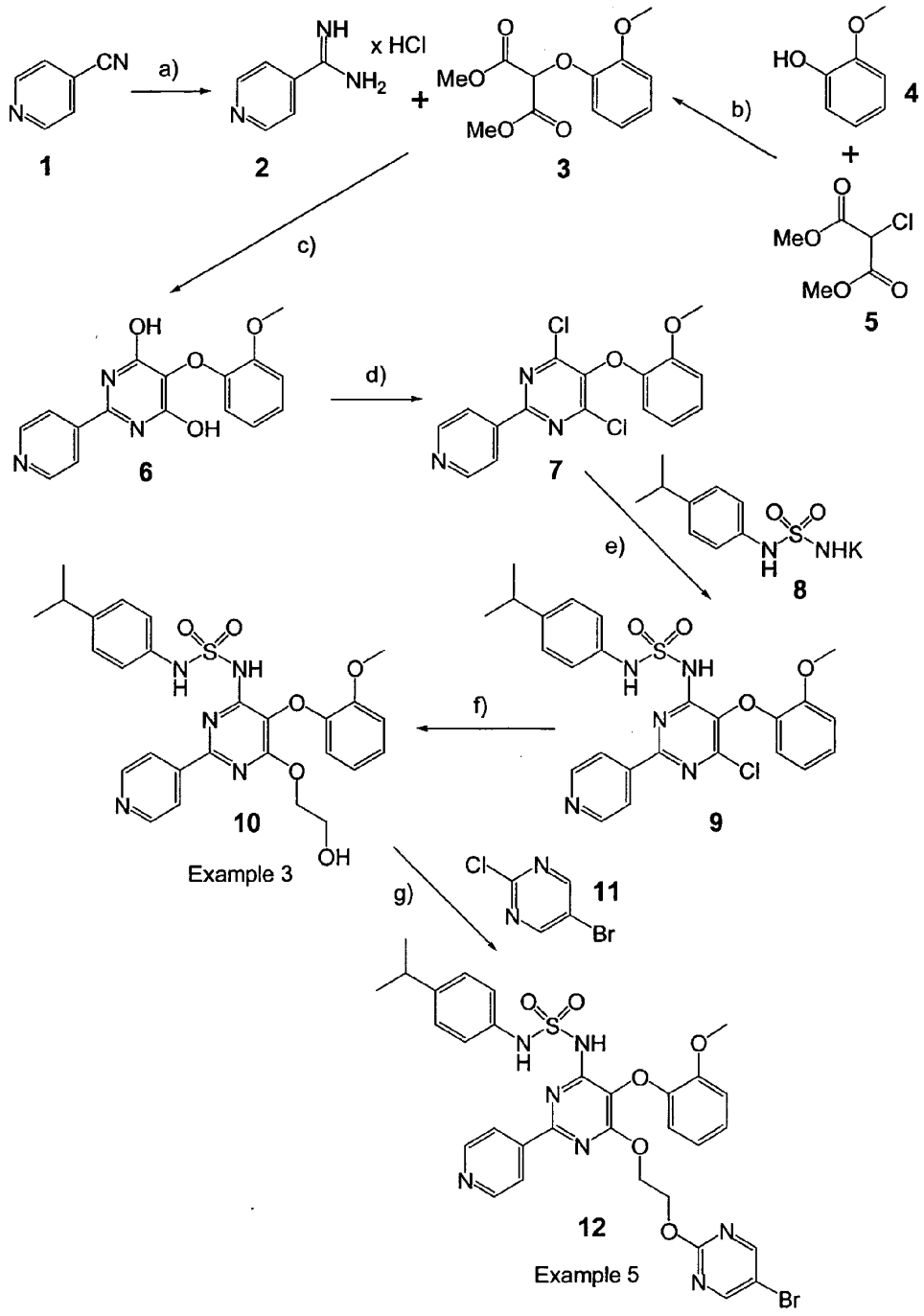
Formula 6

wherein $R^{4'}$ represents:



For possibilities A to C see also [5]

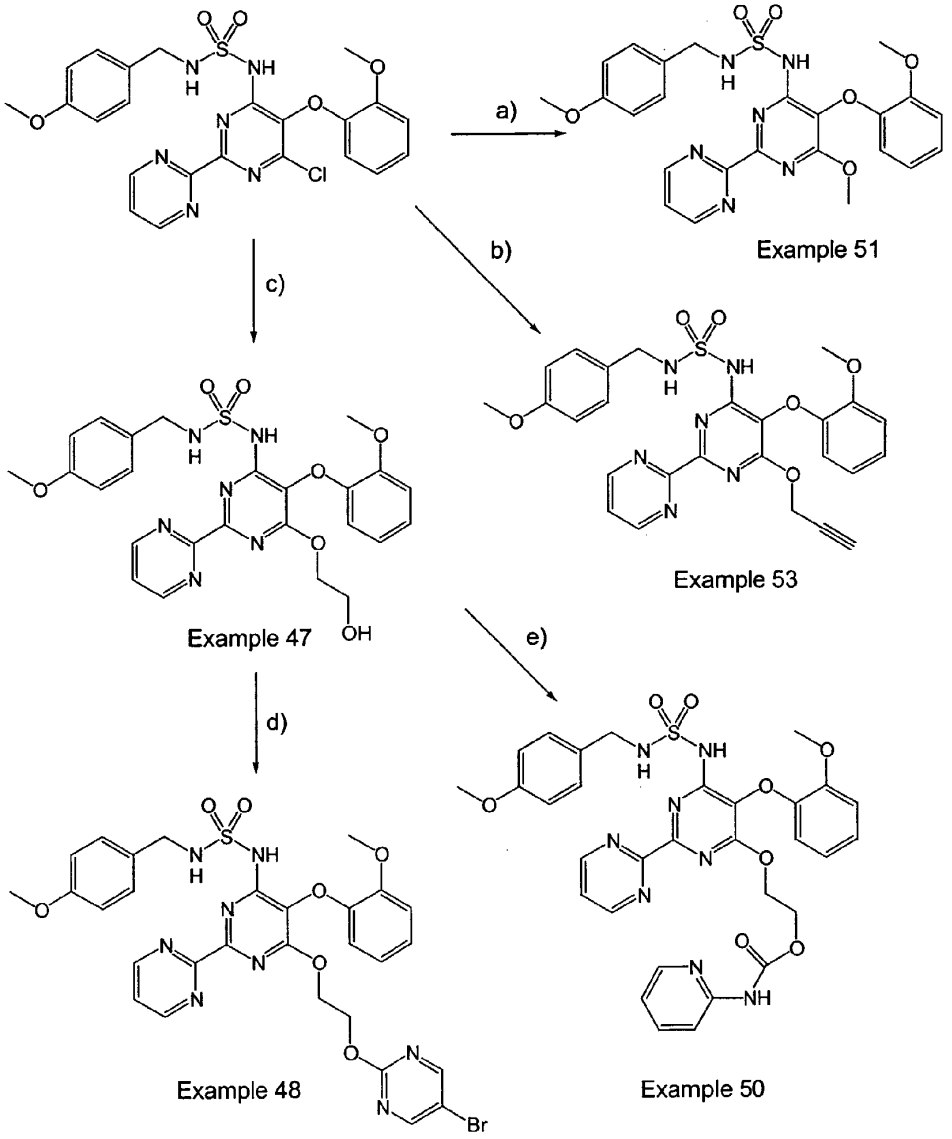
Scheme 1: Schematically exemplified synthesis of Example 3 and Example 5:



a) NaOMe, MeOH then NH_4Cl; b) K_2CO_3, acetone, rflx; c) NaOMe, MeOH; d) $POCl_3$, N,N-dimethylaniline, 70 – 130°C; e) **8**, DMSO; f) Na, ethyleneglycol; 80 – 100°C; g) **11**, THF, NaH, rt – 70°C.

In Scheme 1 the synthetic procedure to prepare compounds of the general formula I is depicted by the description of the synthesis of Example 3 and Example 5. The other examples given in this document can be prepared via the same synthetic pathway, adapting the substituents and reaction conditions. The literature references given in [ ] are set forth at the end of this paragraph. The amidines **2** were synthesized applying standard methodology [1] by reaction of the appropriate nitrile **1** with sodium methylate in methanol followed by addition of ammonium chloride. The 2-substituted malonic esters **3** were prepared according to published procedures [2] by reacting dimethylchloromalonate (**5**) with the appropriate alcohol **4** in acetone and potassium carbonate as base. The compounds **3** were dissolved in methanol, sodium methylate was added, and stirring was continued for about 30 min followed by the addition of an amidine derivative **2**. Stirring at ambient temperature was continued for another 8 h. After acidic work up the 4,6-dihydroxypyrimidines **6** could be isolated in yields of 70 to 90% [2]. Compounds **6** or the tautomeric form thereof were transformed into the dichloro derivatives **7** with phosphorus oxychloride in the presence of N,N-dimethylaniline at elevated temperatures (60-120°C) in yields of 40 to 75% [3]. The dichlorides **7** were reacted with an excess of the appropriate sulfamide potassium salt **8** (prepared as described in Scheme 3) in DMSO at r.t. or 40 to 60°C to give the monochloro-pyrimidines **9** in yields of 70 to 90% either after recrystallization from ethyl acetate / diethylether or chromatography through silica gel with ethyl acetate / heptane. The pyrimidine derivatives **9** are then reacted with ethylene glycol (or another 1-ω-diol, or a mono alcohol) in the presence of a base like potassium tert.-butylate, sodium hydride or sodium at 80 – 110°C for 4 to 16 h to give compounds **10** as the first claimed compounds in yields of 50 to 70%, which can be further transformed to compounds **12** by reaction with 2-chloro-5-bromopyrimidine (**11**) (or another suitable pyrimidine or pyridine derivative) in THF / DMF ~5 / 1 at either r.t. or at 50 – 70°C in yields of 50 – 80%.

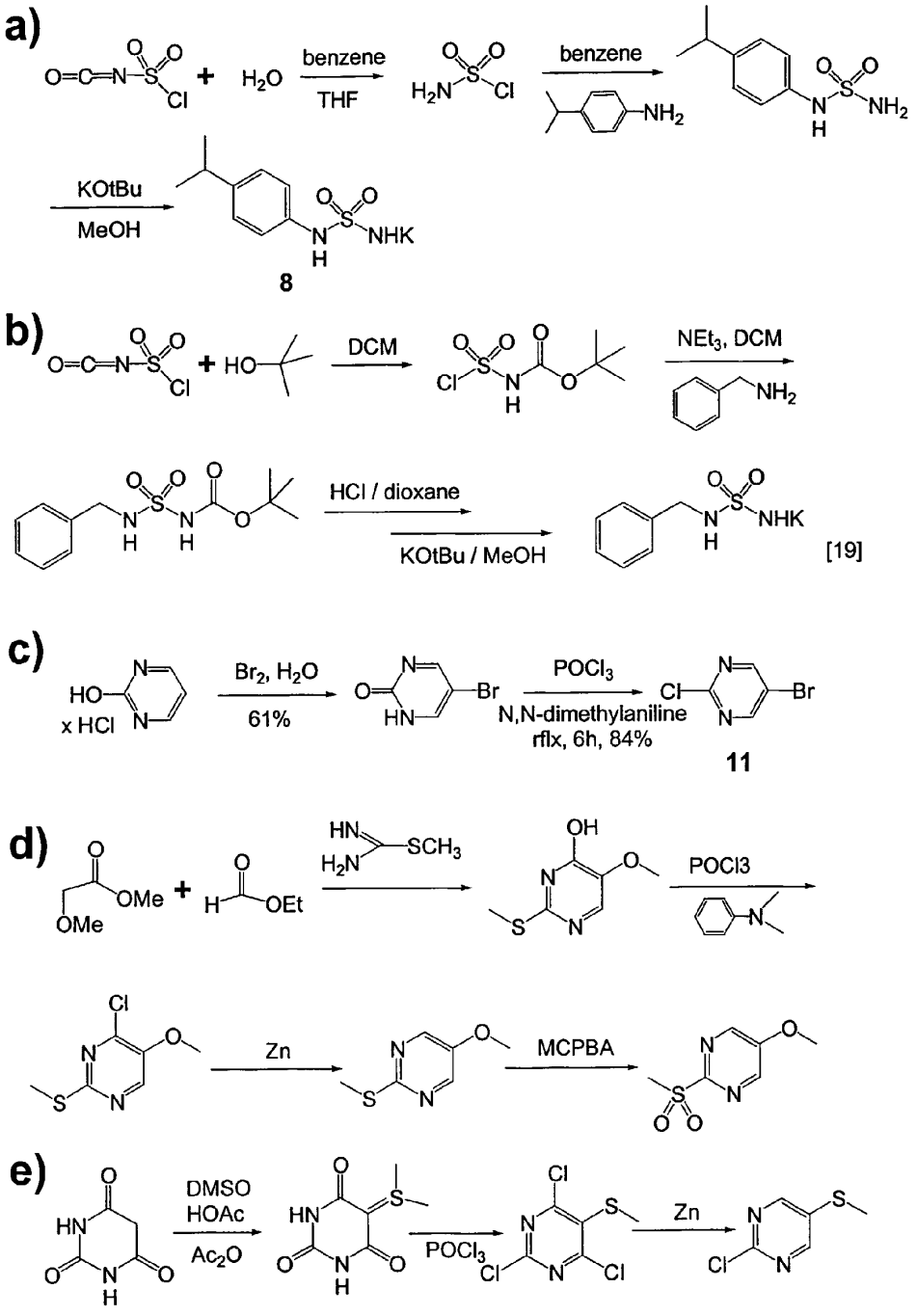
Scheme 2: Schematically exemplified synthesis of Examples 47, 48, 50, 51, 53:



a) NaOMe, MeOH, rflx; b) Propargylic alcohol, NaH, THF, rflx; c) Ethylene glycol, KOtBu, 110°C; d) NaH, THF then 5-bromo-2-chloropyrimidine, 70°C;
e) Pyridine-2-carbonyl azide, CHCl3, 70°C, 2h then Example 47, 70°C, 16h.

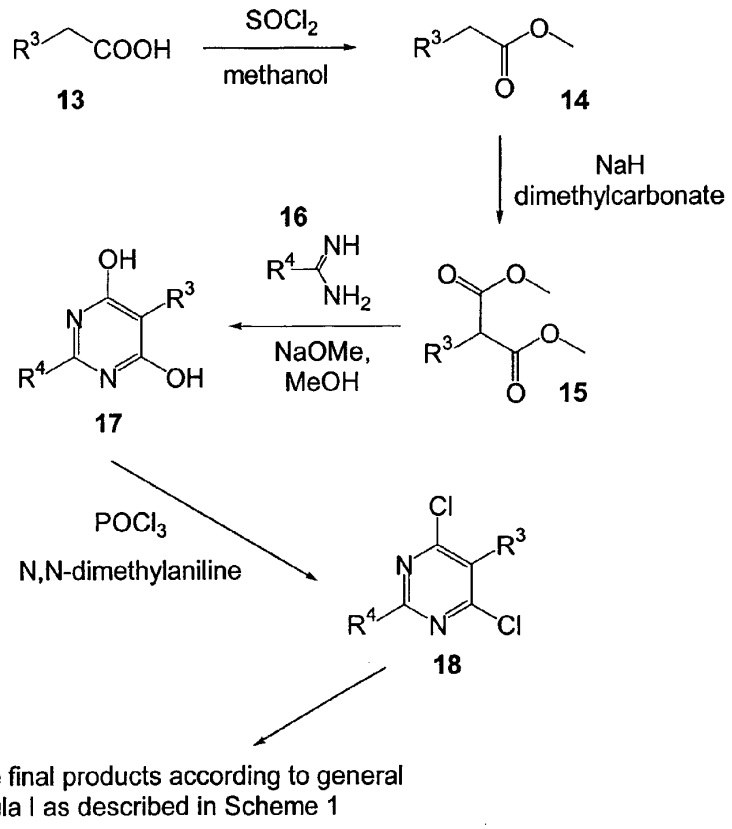
For further experimental descriptions see [1], [2], [3], [5], [6] and [9].

Scheme 3: Preparation of the sulfamide-moieties [10], [11], [12], [13], [14], [15] and [19] and preparation of substituted pyrimidines [16], [17]:



For further experimental descriptions see [1], [2], [3], [5], [6].

Scheme 4: Preparation of the precursors for the synthesis of compounds of general formula I wherein X represents a bond [5], [18]:



In Scheme 4 the symbols represent the same as defined in general formula I above.

[1] W. Göhring, J. Schildknecht, M. Federspiel; *Chimia*, **1996**, *50*, 538 – 543.

[2] W. Neidhart, V. Breu, D. Bur, K. Burri, M. Clozel, G. Hirth, M. Müller, H. P. Wessel, H. Ramuz; *Chimia*, **1996**, *50*, 519 – 524 and references cited there.

[3] W. Neidhart, V. Breu, K. Burri, M. Clozel, G. Hirth, U. Klinkhammer, T. Giller, H. Ramuz; *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 2223 – 2228. R. A. Nugent, S. T. Schlachter, M. J. Murphy, G. J. Cleek, T. J. Poel, D. G. Whishka, D. R. Graber, Y. Yagi, B. J. Keiser, R. A. Olmsted, L. A. Kopta, S. M. Swaney, S. M. Poppe, J. Morris, W. G. Tarpley, R. C. Thomas; *J. Med. Chem.*, **1998**, *41*, 3793 – 3803.

[4] J. March; *Advanced Organic Chemistry*, 4th Ed., **1994**, p. 499 and references cited there.

[5] EP 0 743 307 A1; EP 0 658 548 B1; EP 0 959 072 A1 (Tanabe Seiyaku)

[6] EP 0 633 259 B1; EP 0 526 708 A1; WO 96/19459 (F. Hoffmann-LaRoche)

[7] for the Synthesis of 5-membered heterocycles see: Y. Kohara et al; *J. Med. Chem.*, **1996**, *39*, 5228 – 5235 and references cited there.

[8] EP 0 882 719 A1 (Yamanouchi Pharmaceutical Co., Ltd)

[9] a) R. Graf; *Chem. Ber.*, **1959**, *92*, 509 – 513. b) G. Weiss, G. Schulze; *Liebigs Ann. Chem.*, **1969**, *729*, 40 – 51. c) J. A. Kloek, K. L. Leschinsky, *J. Org. Chem.*, **1976**, *41*, 4028 – 4029. d) R. P. Dickinson, K. N. Dack, C. J. Long, J. Steele; *J. Med. Chem.*, **1997**, *40*, 3442 – 3452. e) E. Cohen, B. Klarberg; *J. Am. Chem. Soc*, **1962**, *84*, 1994 – 2002.

[10] E. Cohen, B. Klarberg; *J. Am. Chem. Soc.*, **1962**, *84*, 1994.

[11] G. Weiss, G. Schulze, *Liebigs Ann. Chem.*, **1969**, *729*, 40.

[12] R. Graf, *Chem. Ber.*, **1959**, *92*, 509.

[13] J. A. Kloek, K. L. Leschinsky, *J. Org. Chem.*, **1976**, *41*, 4028.

[14] R. E. Olson, T. M. Sielecki, et al; *J. Med. Chem.*, **1999**; *42*, 1178.

[15] R. P. Dickinson, K. N. Dack, et al; *J. Med. Chem.*, **1997**; *40*, 3442.

[16] D. G. Crosby, R. V. Berthold; *J. Org. Chem.*, **1960**; *25*; 1916.

[17] Bayer AG (Maurer, F.; Hammann, I.; Behrenz, W.); US-4,233,294 **1980**.

[18] E. D. Morgan; *Tetrahedron*, **1967**, *23*, 1735.

[19] M.J. Tozer, I. M. Buck et al.; *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 3103. G. Dewynter et al.; *Tetrahedron*, **1993**, *49*, 65.

Examples

The following examples illustrate the invention. All temperatures are stated in °C.

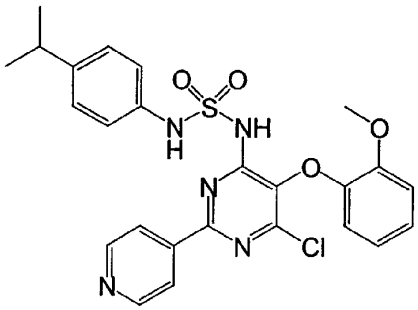
List of Abbreviations:

EtOAc	ethyl acetate
CyHex	cyclohexane
Hex	hexane
DMSO	dimethylsulfoxide
THF	tetrahydrofuran
MCPBA	m-chloroperbenzoic acid
DMF	dimethylformamide
DCM	dichloromethane
HV	high vacuum conditions
rt	room temperature
t_R	retention time
min	minutes
DBU	1,8-diazabicyclo[5.4.0]undec-7-en(1,5-5)
DMAP	4-dimethylaminopyridine
rflx	reflux

The following compounds were prepared according to the procedure described above and shown in *Schemes 1 to 4*. All compounds were characterized by 1H-NMR (300MHz) and occasionally by 13C-NMR (75MHz) (Varian Oxford, 300MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; m = multiplet), by LC-MS (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Column: 2x30mm, Gromsil ODS4, 3µm, 120A; Gradient: 0 – 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45ml/min; t_R is given in min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}) and occasionally by melting point.

Referential Examples (Synthesis of the precursors):

Referential Example 1:



a) To a solution of sodium (0.23 g) in methanol (40 ml) was added 4-cyanopyridine (10.62 g) at r.t.. Stirring was continued for 6 h followed by the addition of ammoniumchloride (5.9 g) and stirring was continued for another 10 h. Then, diethylether (120 ml) was added and the precipitate was filtered off after 30 min and washed with diethylether (20 ml). The product was dried under high vacuum. 4-Amidino-pyridine hydrochloride (14.95 g) was obtained as a white powder.

b) 2-Methoxy-phenol (guaiacol) (48 ml) was slowly added to a stirred suspension of potassium carbonate (70.8 g) in acetone (480 ml) followed by heating to 45°C. Then, dimethylchloromalonate (63.2 ml) in acetone (50 ml) was added within 20 min. The reaction mixture was heated to reflux for 16 h. The solvent was evaporated under reduced pressure, the residue taken into water and extracted with DCM. The combined organic layers were dried over sodium sulfate and evaporated. The oily product was crystallized from tert.-butyl-methyl-ether. Dimethyl-(o-methoxyphenoxy)malonate (86 g) was obtained.

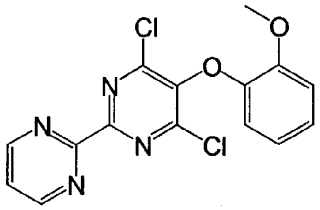
c) To a stirred solution of sodium methylate (9.7 g) in methanol (100 ml) a solution of dimethyl-(o-methoxyphenoxy)malonate (21.7 g) in methanol (50 ml) was added within 15 min and stirring was continued for 30 min followed by the addition of 4-amidino-pyridine hydrochloride (15.0 g) and stirring at r.t. for 20 h. The reaction mixture was concentrated in vacuo. The solid residue was stirred with ether. The

obtained powder was filtered off and dissolved in water (300 ml). Acetic acid was added to pH = 4. The precipitated product was filtered off, washed with water and dried in vacuo at 50°C. 5-(o-Methoxyphenoxy)-4,6-dihydroxy-2-(4-pyridyl)-pyrimidine (20.1 g) (is possibly also present as the tautomeric 5-(o-methoxyphenoxy)-2-(4-pyridyl)-tetrahydropyrimidine-4,6-dion) was obtained as a white powder.

d) 5-(o-Methoxyphenoxy)-4,6-dihydroxy-2-(4-pyridyl)-pyrimidine (10 g), N-diisopropylethylamine (11.2 g), tetraethylammoniumchloride (11 g) and phosphorus pentachloride (13.8 g) were dissolved in phosphorus oxychloride (25 ml) and heated to reflux for 3 h. The mixture was evaporated in vacuo, toluene was added and the mixture was again evaporated. The residue was taken into DCM and poured onto ice/water. The layers were separated, the organic layer was washed with water, dried over sodium sulfate and evaporated. After recrystallization from acetone, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (6.52 g) was obtained.

e) To a solution of 4-i-propyl-phenyl sulfamic acid amide (642 mg; Referential Example 17) in DMF (9 ml) was added sodium hydride (250 mg). The mixture was warmed to 45°C for 30 min. Then, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (1.044 g) was added and the reaction mixture was stirred for 60 h at r.t.. After acidic work up and chromatography over silicagel with Hex / EtOAc = 2 / 5, 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (0.42 g) can be isolated.

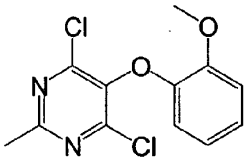
Referential Example 2:



a) 4,6-Dihydroxy-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine [or its tautomer 5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-tetrahydropyrimidine-4,6-dion] was prepared as disclosed in EP 0 526 708 A1 from 2-amidino-pyrimidine and dimethyl-(o-methoxyphenoxy)malonate.

b) 4,6-Dichloro-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine was prepared as disclosed in EP 0 526 708 A1 from 4,6-dihydroxy-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-pyrimidine (which may also be present in the tautomeric form 5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-tetrahydro-pyrimidine-4,6-dione).

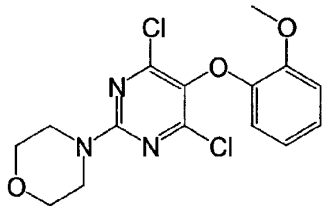
Referential Example 3:



a) A solution of dimethyl-(o-methoxyphenoxy)malonate (10 g) in dry methanol (80 ml) was cooled to 0°C. Sodium methylate (6.71 g) was added portionwise. To the suspension was added of acetamidine hydrochloride (2.84 g) and the mixture was stirred overnight at r.t.. The solvent was removed under reduced pressure and the residue was suspended in diethyl ether (100 ml). The solid was filtered off, washed with another portion of diethyl ether (100 ml) and dissolved in water (50 ml). The pH was adjusted to 4 by adding glacial acetic acid (25 ml). The white precipitate that formed was filtered off, washed with water and dried to yield 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-methyl-pyrimidine (5.17 g) (or a tautomer) as a white powder.

b) A solution of 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-methyl-pyrimidine (10.9 g) (or a tautomer) in $POCl_3$ (150 ml) was stirred at 50°C for 72 h. The excess of $POCl_3$ was evaporated, toluene was added to coevaporate traces of $POCl_3$. Eventually, an ice/water mixture was carefully added to the residue and the pH was adjusted to 8 using 3 N sodium hydroxide solution. The mixture was further diluted with water (300 ml) and extracted with DCM (500 ml). The organic layer was separated, washed with water (300 ml), dried over Na_2SO_4 and evaporated. The residue was dissolved again in DCM and filtered through a pad of silica gel eluting with DCM. The solvent was removed in vacuo. The resulting residue was dried to furnish 4,6-dichloro-5-(o-methoxyphenoxy)-2-methyl-pyrimidine (8.7 g) as a beige powder.

Referential Example 4:

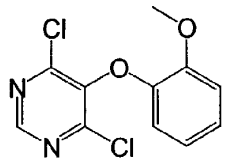


a) A solution of dimethyl-(o-methoxyphenoxy)malonate (32.75 g) in methanol (250 ml) was cooled to 0°C. Sodium methylate (20.0 g) was added portionwise and upon completion of the addition the mixture was stirred at r.t. for 6 h. Then morpholinoformamidine hydrobromide (25.0 g) was added and stirring was continued for 72 h. The solvent of the beige suspension was evaporated and the residue was washed twice with diethyl ether (150 ml). The remaining powder was dissolved in water (200 ml). Upon adjusting the pH to 4 with acetic acid (50 ml) a precipitate formed. The precipitate was collected, washed with water and dried under high vacuum to yield 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-(N-morpholino)-pyrimidine (17.01 g) (or a tautomer) as a slightly beige powder.

b) At 0°C $POCl_3$ (50 ml) was carefully added to Hünig's base (27.5 ml). To this mixture 5-(o-methoxyphenoxy)-4,6-dihydroxy-2-(N-morpholino)-pyrimidine (17 g) was added portionwise. The resulting mixture was stirred over night at 130°C. The excess of reagents was evaporated and traces of $POCl_3$ were removed by

coevaporation with toluene. The black residue was treated with DCM (50 ml) and a water/ice mixture (50 ml). After stirring for 15 min, the mixture was diluted with water (400 ml) and DCM (400 ml). The organic layer was separated and washed with water (300 ml). The aqueous layer was extracted with DCM (400 ml). The combined DCM layers were dried over Na_2SO_4 and the solvent was removed to a volume of about 100 ml. The remaining solution was filtered over silica gel (50 g) eluting with DCM. The filtrate was evaporated. The resulting residue was suspended in diethyl ether (50 ml). The solid was filtered off and dried to give 4,6-dichloro-5-(o-methoxyphenoxy)-2-(N-morpholino)-pyrimidine (13.85 g) as a white crystalline powder.

Referential Example 5:

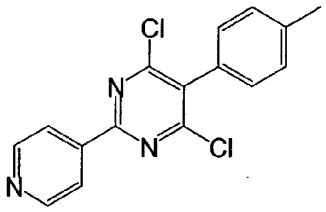


a) At 5°C sodium methylate (12.7 g) was added portionwise to a solution of dimethyl-(o-methoxyphenoxy)malonate (18.9 g) in methanol (450 ml). Upon completion of the addition stirring was continued at r.t. for 30 min followed by the addition of formamidine hydrochloride (6 g). The mixture was stirred at r.t. for 72 h. Eventually, the solvent was removed under reduced pressure and the remaining residue was suspended in diethyl ether. The solid material was filtered off and dissolved in water (100 ml). The solution was acidified with conc. hydrochloric acid. A white precipitate formed. The precipitate was collected, washed with water and dried to give 5-(o-methoxyphenoxy)-4,6-dihydroxy-pyrimidine (15.1 g) (or a tautomer) as a white powder.

b) To a solution of 5-(o-methoxyphenoxy)-4,6-dihydroxy-pyrimidine (7.5 g) in $POCl_3$ (90 ml) N,N-dimethylaniline (24 ml) was added. The mixture was heated to 160°C and stirred for 2.5 h. Excess of $POCl_3$ was distilled off under reduced pressure. Traces of $POCl_3$ were coevaporated with toluene. The remaining oil was treated with a water:ice mixture. The mixture was acidified with 1 N hydrochloric acid and extracted twice with diethyl ether. The combinded organic layers were

washed twice with dilute aqueous hydrochloric acid, dried over $MgSO_4$ and evaporated. The remaining solid was washed with methanol and dried. This gave 4,6-dichloro-5-(o-methoxyphenoxy)-pyrimidine (4.75 g) as a pale yellow powder.

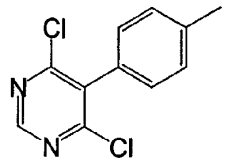
Referential Example 6:



a) A solution of sodium methylate (6.8 g) in methanol (200 ml) was cooled to 0°C. A solution of diethyl 2-(p-tolyl)-malonate (10.3 g) in methanol (50 ml) was slowly added. Upon completion of the addition the solution was allowed to warm to r.t. and 4-amidino-pyridine hydrochloride (7.57 g) was added. The mixture was stirred at r.t. for 16 h. Eventually, the solvent was removed under reduced pressure and the remaining residue was dissolved in 2 M hydrochloric acid. The solution was extracted with diethyl ether, then adjusted to pH 5 with 10 M sodium hydroxide solution. A precipitate formed. The precipitate was collected, washed with cold water and dried at 60°C under high vacuum. This gave 4,6-dihydroxy-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (8.77 g) (or a tautomer) as orange crystals.

b) To a mixture of 4,6-dihydroxy-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (8.0 g) and $POCl_3$ (100 ml) diethylamine (25 ml) was added at r.t.. The mixture was stirred for 16 h at 60°C. The excess of $POCl_3$ was distilled off under reduced pressure. The remaining oil was dissolved in DCM (300 ml) and treated with water (300 ml). The aqueous layer was separated and extracted three times with DCM. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and evaporated. The resulting residue was suspended in isopropanol. The solid material was collected, washed with isopropanol and diethyl ether and dried to give 4,6-dichloro-2-(4-pyridyl)-5-(p-tolyl)-pyrimidine (7.2 g) as a white crystalline powder.

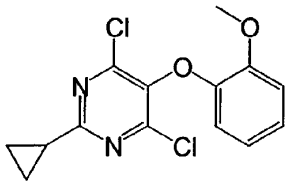
Referential Example 7:



a) At 0°C a solution of diethyl 2-(p-tolyl)-malonate (14.2 g) in methanol (50 ml) was slowly added to a solution of sodium methylate (9.4 g) in methanol (300 ml). Upon completion of the addition the reaction mixture was allowed to warm up and formamidine hydrochloride (5.4 g) was added. The mixture was stirred at r.t. for 16 h. The solvent was removed under reduced pressure and the remaining residue was treated with 2 N hydrochloric acid (150 ml). The suspension was stirred for 0.5 h. At 0-5°C, the pH was carefully adjusted to 4 using 10 N sodium hydroxide solution. The precipitate was collected, washed with cold water, isopropanol, and diethyl ether and dried under high vacuum at 65°C to give 4,6-dihydroxy-5-(p-tolyl)-pyrimidine (11.2 g) (or a tautomer) as a white powder.

b) At r.t. N,N-dimethylaniline (10 ml) was added to a mixture of 4,6-dihydroxy-5-(p-tolyl)-pyrimidine (5.1 g) and $POCl_3$ (75 ml). The reaction mixture was stirred at 70°C for 16 h. The excess of $POCl_3$ was distilled off and the remaining oil was treated with an ice:water mixture and extracted three times with diethyl ether. The combined organic layers were washed with 1N aqueous hydrochloric acid followed by brine, dried over $MgSO_4$ and evaporated. The remaining brown oil was crystallised from isopropanol. The pale yellow crystals were collected, washed with cold isopropanol and dried under high vacuum to furnish 4,6-dichloro-5-(p-tolyl)-pyrimidine (4.1 g).

Referential Example 8:

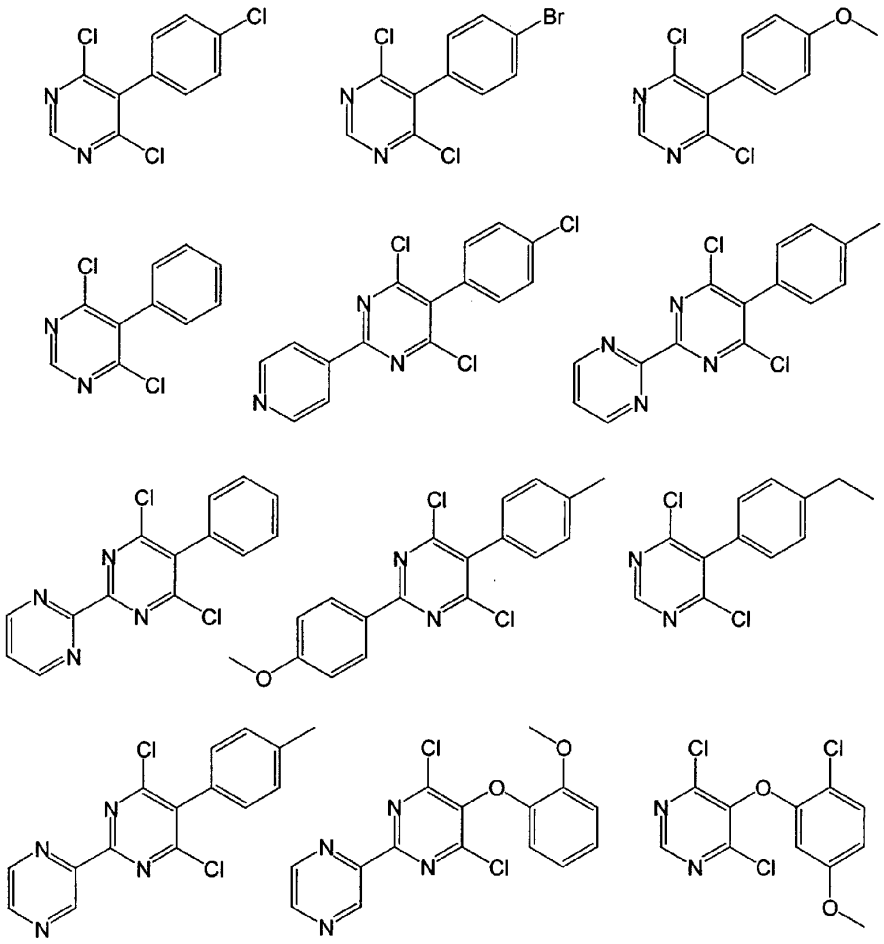


a) To a solution of sodium (5.17 g) in methanol (200 ml) dimethyl-(2-methoxyphenoxy)malonate (21.1 g) was added and the mixture was stirred at r.t. for 30 min. To the slurry, cyclopropylamidine hydrochloride (12.0 g) was added. The mixture was stirred at r.t. for 22 h. Eventually, the solvent was removed in vacuo. The remaining residue was suspended in diethyl ether (250 ml). The diethyl ether was decanted and the remaining solid was dissolved in water (250 ml). The solution was acidified with 25% aqueous hydrochloric acid. The precipitate that formed was collected, washed with water and dried at 60°C under high vacuum to give 5-(2-methoxyphenoxy)-4,6-dihydroxy-2-cyclopropyl-pyrimidine (19.26 g) as a colourless powder. LC-MS: t_R = 2.74 min, $[M+1]^+$ = 275.24, $[M-1]^-$ = 273.29.

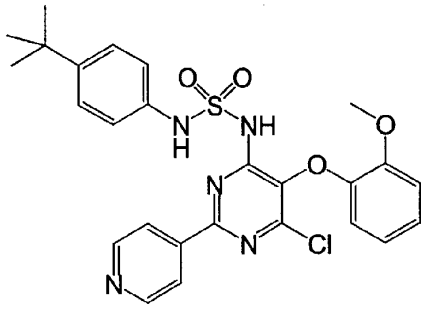
b) To a suspension of 5-(2-methoxyphenoxy)-4,6-dihydroxy-2-cyclopropyl-pyrimidine (8.22 g) in $POCl_3$ (87 ml), N,N-dimethylaniline (12 ml) was added. The mixture became clear and was stirred at 130°C for 3.5 h. Excess $POCl_3$ was removed in vacuo, remaining traces of $POCl_3$ were coevaporated with toluene. The remaining sirup was poured on an ice-water mixture and the resulting solution was extracted three times with diethyl ether. The organic layers were combined, washed once with 1 N aqueous hydrochloric acid and twice with water, treated with activated charcoal, dried over $MgSO_4$ and evaporated. The residue was crystallised from a diethyl ether/hexane to give 4,6-dichloro-2-cyclopropyl-5-(2-methoxyphenoxy)-pyrimidine (6.64 g) as a beige powder. LC-MS: t_R = 5.36 min, $[M+1]^+$ = 311.19.

Referential Example 9:

According to procedures described in **Referential Examples 1 to 8** and in the literature [2], [3], [5], [6] and [8], the following 4,6-dichloropyrimidine precursors were prepared.

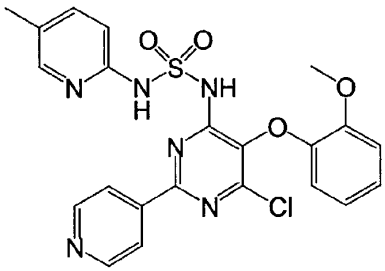


Referential Example 10:



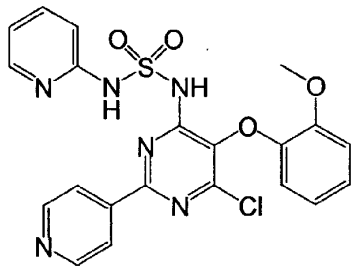
To a solution of 4-t-butyl-phenyl sulfamic acid amide (228 mg, Referential Example 18) in DMF (3 ml) was added sodium hydride (42 mg). Then, 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (305 mg) and Hünig base (0.17 ml) was added and the reaction mixture was stirred for 5 h at 60°C. After acidic work up and crystallization, 4-t-butyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (0.15 g) could be isolated. t_R = 5.54 min (LC); $[M+H]^+$ = 540.44 (ES+);

Referential Example 11:



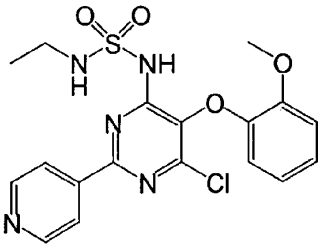
According to the procedure described in referential Example 1e), 5-methyl-pyridine-2-sulfamic acid amide (252 mg, Referential Example 20) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (410 mg, Referential Example 1d)) to give 5-methyl-pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (100 mg). t_R = 4.02 min (LC); $[M+H]^+$ = 499.33 (ES+);

Referential Example 12:



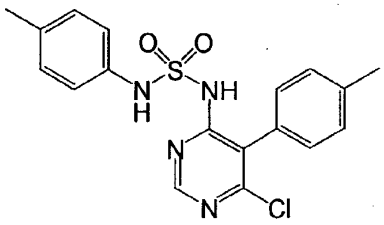
According to the procedure described in referential Example 1e), pyridine-2-sulfamic acid amide (60 mg, Referential Example 21) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg, Referential Example 1d)) to give pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (100 mg). t_R = 3.83 min (LC); $[M-H]^+$ = 483.33 (ES-);

Referential Example 13:



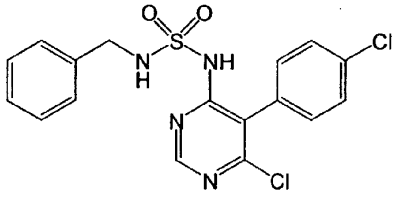
According to the procedure described in referential Example 1e), ethyl-sulfamic acid amide (40 mg, Referential Example 22) was reacted with 4,6-dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg, Referential Example 1d)) to give pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (70 mg). t_R = 4.40 min (LC); $[M-H]^+$ = 434.28 (ES-);

Referential Example 14:



To 4,6-dichloro-5-p-tolyl-pyrimidine (Referential Example 7) (2.0 g) dissolved in DMSO (35 ml) was added di-isopropyl-ethyl-amine (1.46 ml) followed by addition of 4-methyl-phenyl sulfamic acid amide potassium salt (2.78 g) [prepared from the product described in Referential Example 19 and potassium tert.-butylate in methanol followed by evaporation of the solvent]. The mixture was stirred for 48 h at rt then poured onto water (500 ml) and diethylether (250 ml) was added and the solution was stirred for 30 min. The layers were separated and the water layer was acidified with acetic acid (2.0 ml) and cooled to 0°C for 1 h. The precipitated product was filtered off and washed with water and diethylether and dried to give 4-methyl-phenyl sulfamic acid-[6-chloro-5-(p-tolyl)-4-pyrimidinyl]-amide (2.02 g). t_R = 5.00 min (LC); $[M+H]^+$ = 389.11 (ES+);

Referential Example 15:



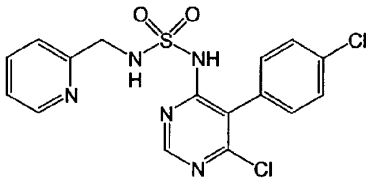
To 4,6-dichloro-5-(4-chloro-phenyl)-pyrimidine (Referential Example 9) (2.59 g) dissolved in DMSO (14 ml) was added di-isopropyl-ethyl-amine (1.8 ml) followed by the addition of benzyl sulfamic acid amide potassium salt (2.25 g) [prepared from the product described in Referential Example 22 and potassium tert.-butylate in methanol followed by the evaporation of the solvent]. The mixture was stirred for 24 h at rt then poured onto water (300 ml) and diethylether (120 ml) was added and the solution was stirred for 30 min. The layers were separated and the water

layer was acidified with solid citric acid (pH = 3) and cooled to 0°C for 1 h. The precipitated product was filtered off, washed with water and recrystallized from methanol to give benzyl sulfamic acid-[6-chloro-5-(p-chloro-phenyl)-4-pyrimidinyl]-amide (1.8 g). t_R = 4.94 min (LC); $[M+H]^+$ = 410.90 (ES+);

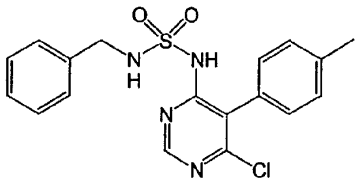
UNITED THERAPEUTICS CORP., EX1003, page 75
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Referential Example 16:

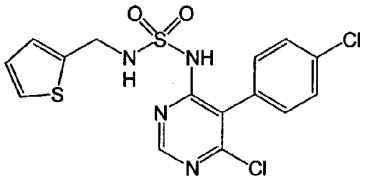
According to the procedure described for the synthesis of **Referential Example 15**, the following compounds could be prepared:



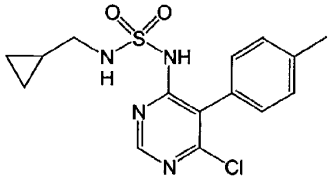
LC-MS:t_R: 4.00; $[M+H]^+$: 411.96



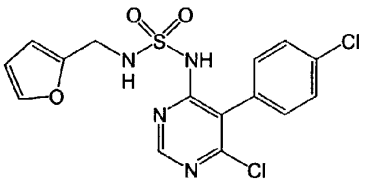
LC-MS:t_R: 4.98 ; $[M+H]^+$: 389.91



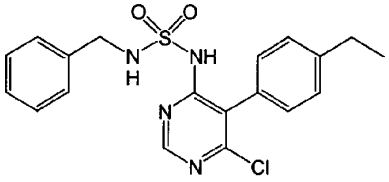
LC-MS:t_R: 4.84; $[M+H]^+$: 414.77



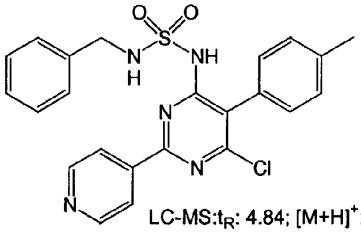
LC-MS:t_R: 4.76; $[M-H]^+$: 351.03



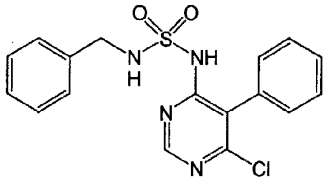
LC-MS:t_R: 4.66; $[M+H]^+$: 400.88



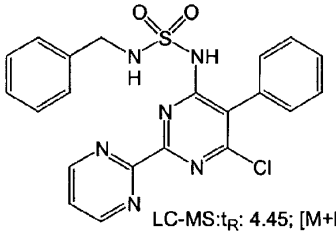
LC-MS:t_R: 5.10; $[M+H]^+$: 403.05



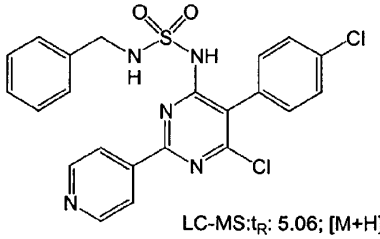
LC-MS:t_R: 4.84; $[M+H]^+$: 466.11



LC-MS:t_R: 4.65; $[M+H]^+$: 375.05

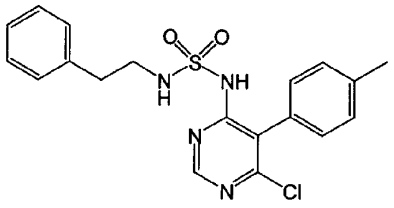


LC-MS:t_R: 4.45; $[M+H]^+$: 453.03

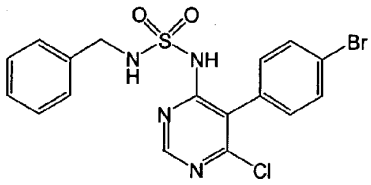


LC-MS:t_R: 5.06; $[M+H]^+$: 486.01

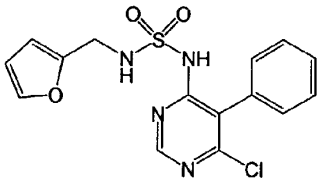
Referential Example 16 (continued):



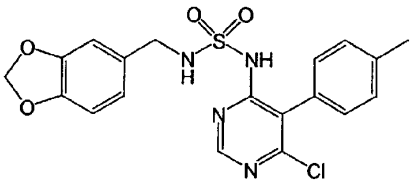
LC-MS:t_R: 5.08; $[M+H]^+$: 403.03



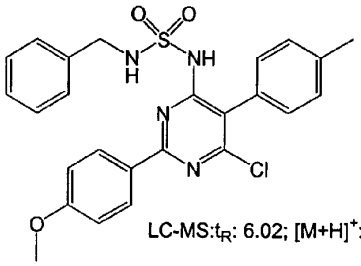
LC-MS:t_R: 5.05; $[M+H]^+$: 454.99



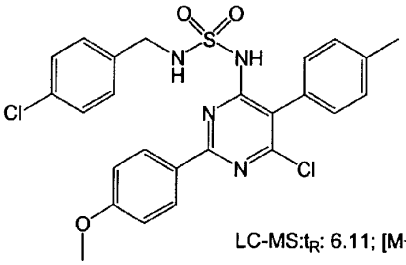
LC-MS:t_R: 4.31; $[M+H]^+$: 365.36



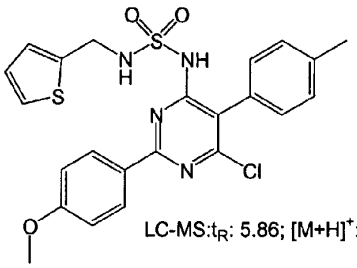
LC-MS:t_R: 4.84; $[M-H]^+$: 433.05



LC-MS:t_R: 6.02; $[M+H]^+$: 495.30

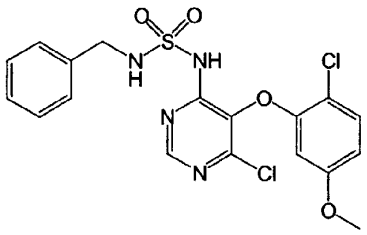


LC-MS:t_R: 6.11; $[M+H]^+$: 529.28

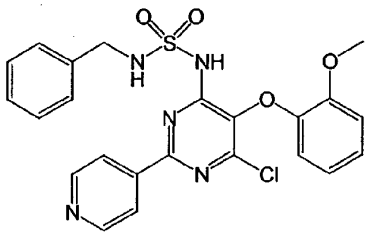


LC-MS:t_R: 5.86; $[M+H]^+$: 501.08

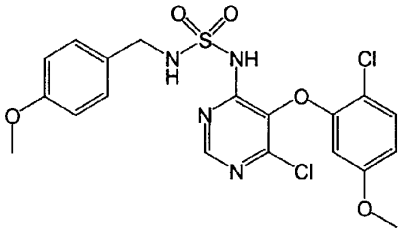
Referential Example 16 (continued):



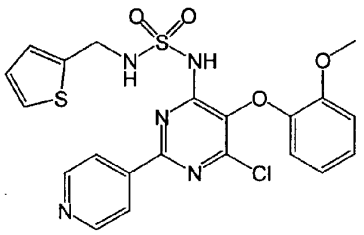
LC-MS:t_R: 5.13; $[M+H]^+$: 456.91



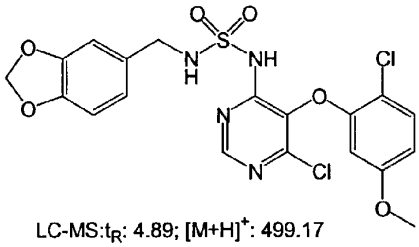
LC-MS:t_R: 4.68; $[M+H]^+$: 498.14



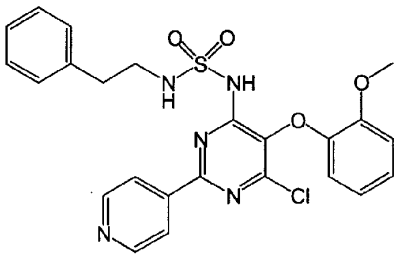
LC-MS:t_R: 4.93; $[M+H]^+$: 484.95



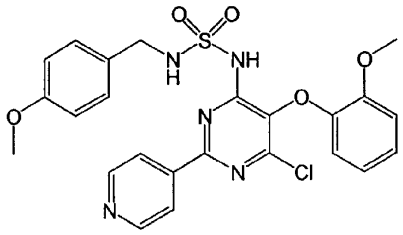
LC-MS:t_R: 4.57; $[M+H]^+$: 504.06



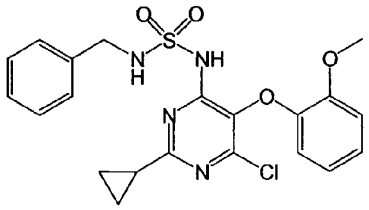
LC-MS:t_R: 4.89; $[M+H]^+$: 499.17



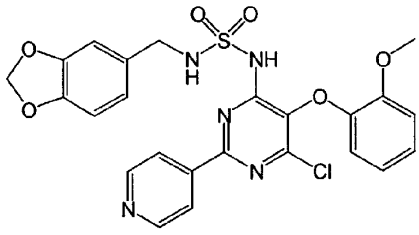
LC-MS:t_R: 4.90; $[M+H]^+$: 512.18



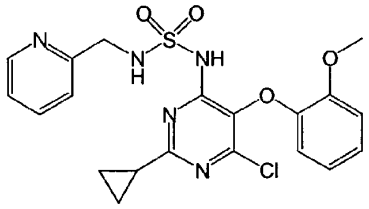
LC-MS:t_R: 4.72; $[M+H]^+$: 527.94



LC-MS:t_R: 5.28; $[M+H]^+$: 461.16

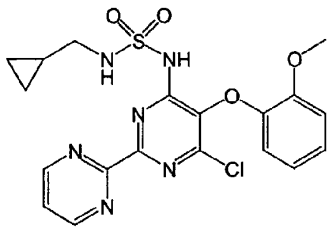


LC-MS:t_R: 4.63; $[M+H]^+$: 542.08

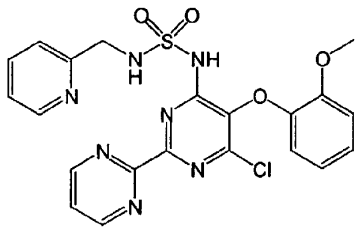


LC-MS:t_R: 3.91; $[M+H]^+$: 462.17

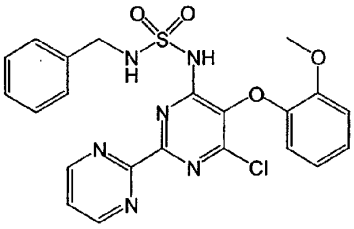
Referential Example 16 (continued):



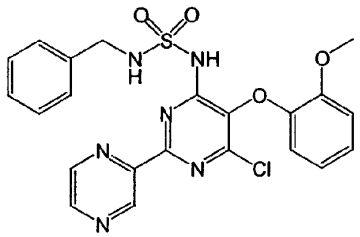
LC-MS:t_R: 4.43; $[M+H]^+$: 463.09



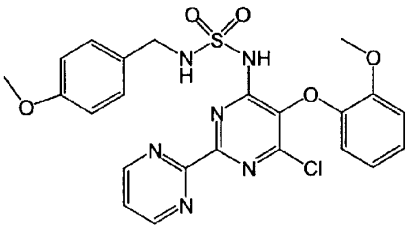
LC-MS:t_R: 3.20; $[M-H]^+$: 497.93



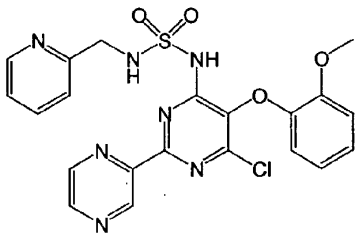
LC-MS:t_R: 4.47; $[M+H]^+$: 499.11



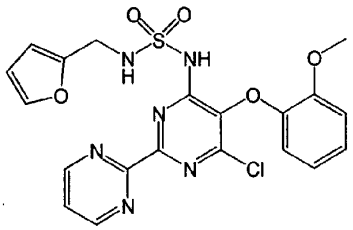
LC-MS:t_R: 4.90; $[M+H]^+$: 499.06



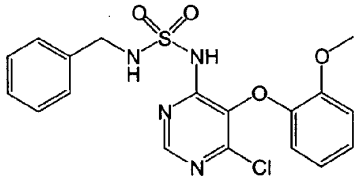
LC-MS:t_R: 4.44; $[M+H]^+$: 529.22



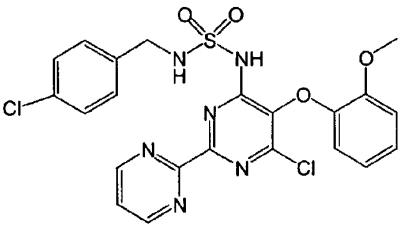
LC-MS:t_R: 3.94; $[M+H]^+$: 500.06



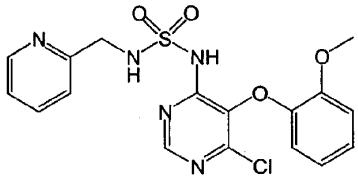
LC-MS:t_R: 4.33; $[M+H]^+$: 489.51



LC-MS:t_R: 4.68; $[M+H]^+$: 421.09

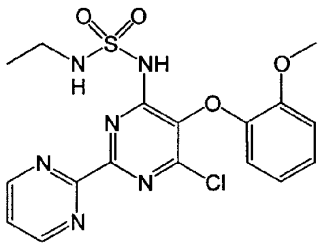


LC-MS:t_R: 4.74; $[M+H]^+$: 535.06

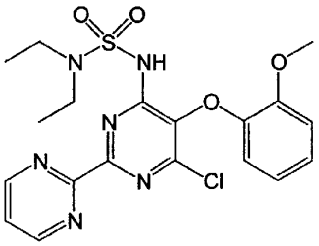


LC-MS:t_R: 3.70; $[M+H]^+$: 423.05

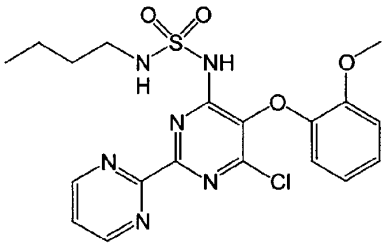
Referential Example 16 (continued):



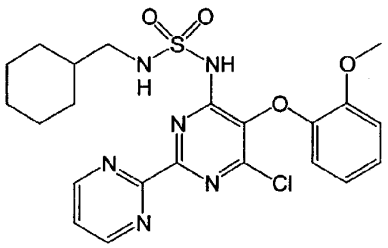
LC-MS:t_R: 3.98; $[M+H]^+$: 437.07



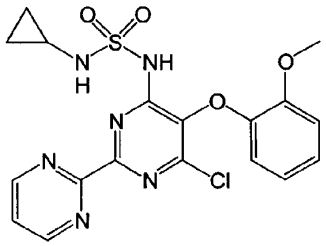
LC-MS:t_R: 4.53; $[M+H]^+$: 465.22



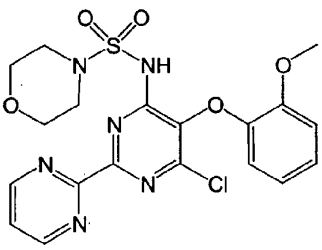
LC-MS:t_R: 5.51; $[M+H]^+$: 465.15



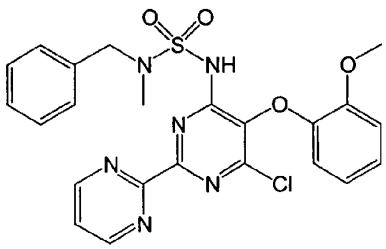
LC-MS:t_R: 5.14; $[M+H]^+$: 505.20



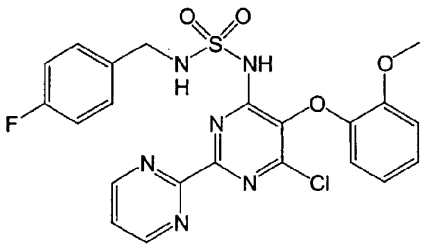
LC-MS:t_R: 4.23; $[M+H]^+$: 449.17



LC-MS:t_R: 4.08; $[M+H]^+$: 479.22

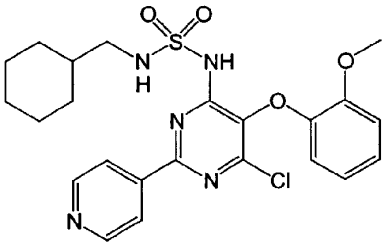


LC-MS:t_R: 5.07; $[M+H]^+$: 513.19

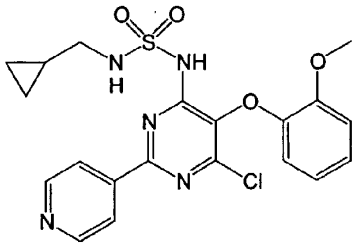


LC-MS:t_R: 4.67; $[M+H]^+$: 517.26

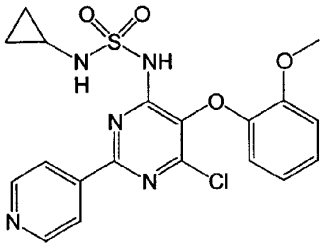
Referential Example 16 (continued):



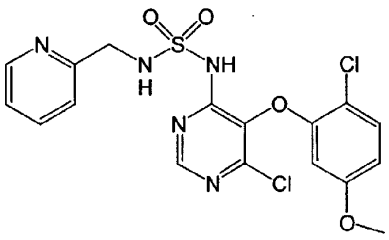
LC-MS:t_R: 5.36; $[M+H]^+$: 505.63



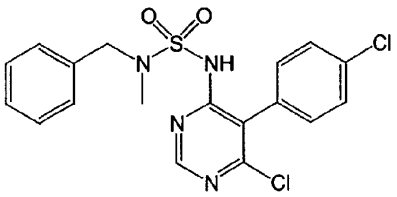
LC-MS:t_R: 4.69; $[M+H]^+$: 462.23



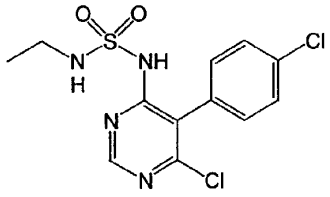
LC-MS:t_R: 4.38; $[M+H]^+$: 448.27



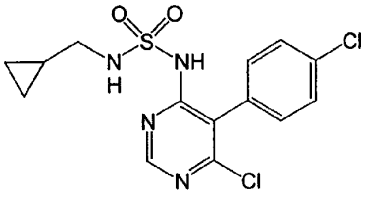
LC-MS:t_R: 4.09; $[M+H]^+$: 456.21



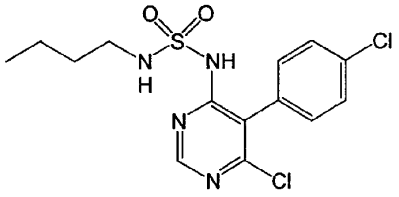
LC-MS:t_R: 5.48; $[M+H]^+$: 424.80



LC-MS:t_R: 4.42; $[M+H]^+$: 347.03

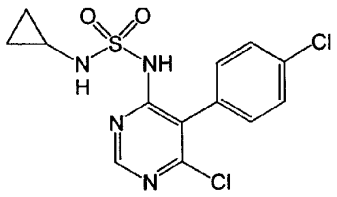


LC-MS:t_R: 4.85; $[M+H]^+$: 375.03

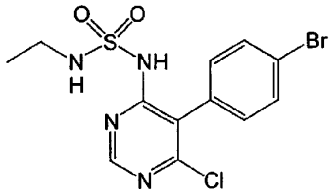


LC-MS:t_R: 4.94; $[M+H]^+$: 376.65

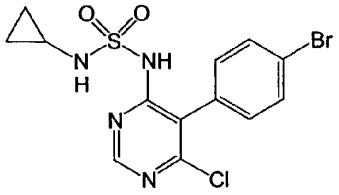
Referential Example 16 (continued):



LC-MS:t_R: 4.61; $[M+H]^+$: 360.99



LC-MS:t_R: 4.41; $[M+H]^+$: 392.95

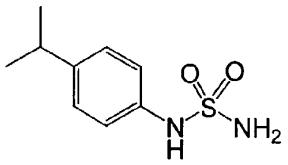


LC-MS:t_R: 4.94; $[M+H]^+$: 404.97

Synthesis of the sulfamic acid amides:

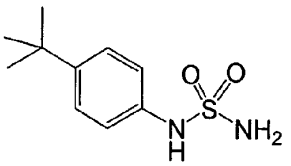
Sulfamoylchloride (NH_2-SO_2-Cl) was prepared according to the procedure given in the literature [11] and [12].

Referential Example 17:



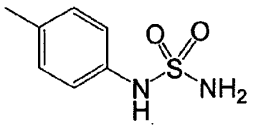
To a solution of sulfamoylchloride in benzene (0.09 mol in 70 ml) was added 4-i-propyl aniline (25.6 ml) via addition funnel at 0°C. The suspension was diluted with benzene (80 ml) and stirred for 20 min. $NaOH_{aq}$ (36 ml; 5 N) was added and the suspension was thoroughly shaken. EtOAc (500 ml) was added and under ice cooling conc. hydrochloric acid was added until pH = 6. The water was separated and the EtOAc was evaporated. The brown residue was shaken twice with hexane followed by the addition of a sodium hydroxide solution (5 N). The mixture was extracted three times with diethylether. The water layer was cooled to 0°C and the pH adjusted to 2 by the addition of conc. hydrochloric acid. The product precipitated and was filtered off and washed with cold water. After high vacuum drying 4-isopropyl-phenyl-sulfamic acid amide was obtained (3.47 g).

Referential Example 18:



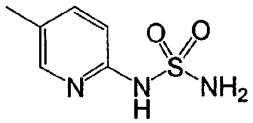
According to the procedure described in Referential Example 17, 4-tert.-butyl-phenyl-sulfamic acid amide was prepared.

Referential Example 19:



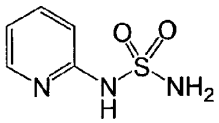
According to the procedure described in Referential Example 17, 4-methyl-phenyl-sulfamic acid amide was prepared.

Referential Example 20:



To a solution of 2-amino-5-methyl-pyridine (3.24 g) in THF (30 ml) was added sodium hydride (1.2 g; 60% disperison in mineral oil). The mixture was warmed to 45°C for 30 min. After cooling to 10°C a solution of sulfamoylchloride in diethylether (0.0445 mol in 62.5 ml) was added within 30 min followed by stirring for 30 min at r.t. and evaporation of the solvent. To the residue was added a sodium hydroxide solution (5 N, 15 ml). The mixture was extracted several times with toluene. The water layer was cooled to 0°C and the pH was adjusted to 7 by the addition of conc. hydrochloric acid. The product crystallized and was filtered off to give 5-methyl-pyridine-2-sufamic acid amide (1.1 g).

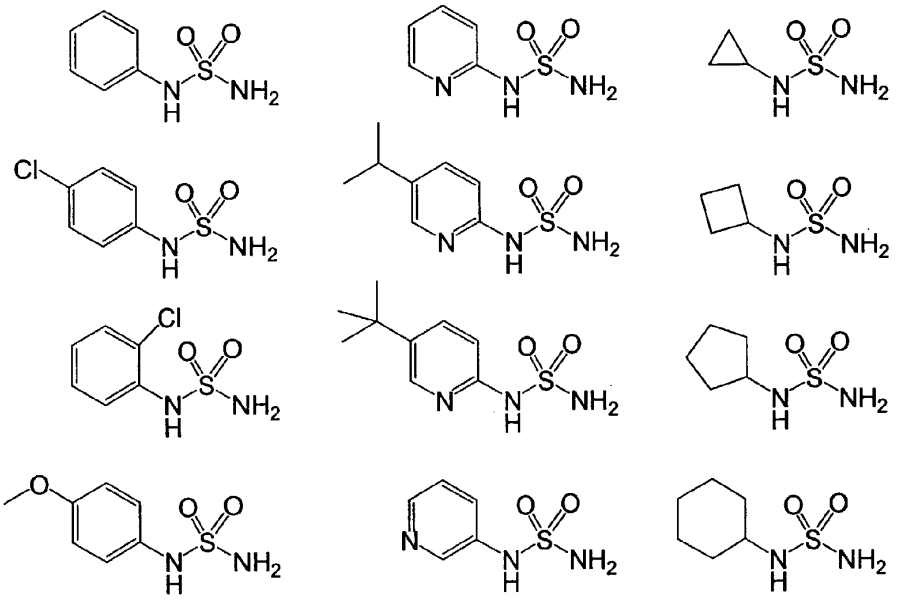
Referential Example 21:



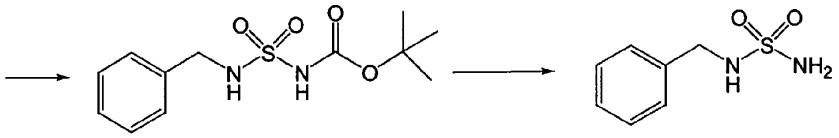
According to the procedure described in Referential Example 20, pyridine-2-sulfamic acid amide was prepared.

Further cycloalkyl-, aryl- or heteroaryl-sulfamic acid amides (as given by the formulae in ***Figure 1***) can be prepared according to the procedure described in **Referential Example 17** (for cycloalkyl and aryl derivatives) or according to the procedure described in **Referential Example 21** (for heteroaryl derivatives) or according to the procedure described in **Referential Example 22** (for cycloalkyl derivatives).

Figure 1:



Referential Example 22: [19]



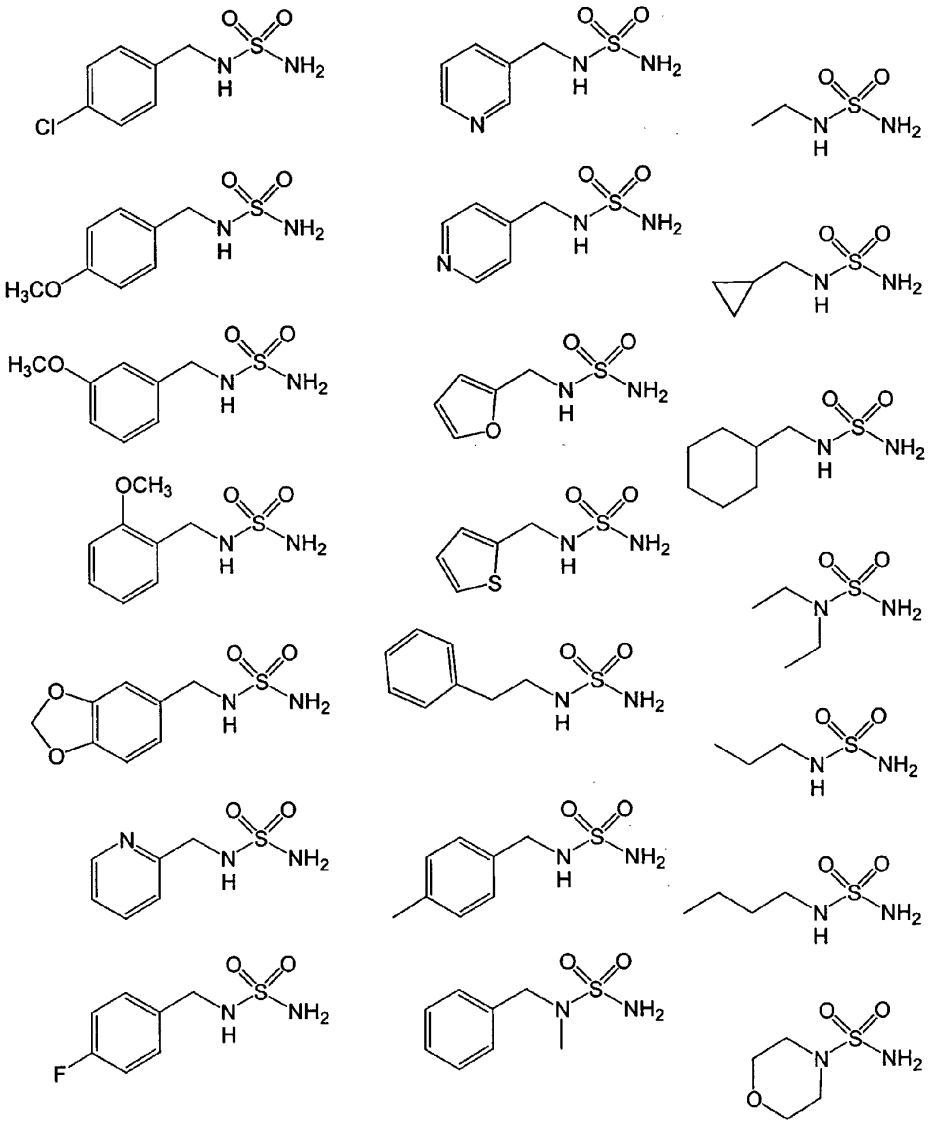
ZP1 Benzylsulfamide

a) Chlorosulfonylisocyanate (14.14 g) was dissolved in DCM (50 ml) and cooled to 0°C. A solution of tert.-butanol (9.6 ml) in DCM (50 ml) was added within 30 minutes. Stirring was continued for additional 30 minutes at rt.

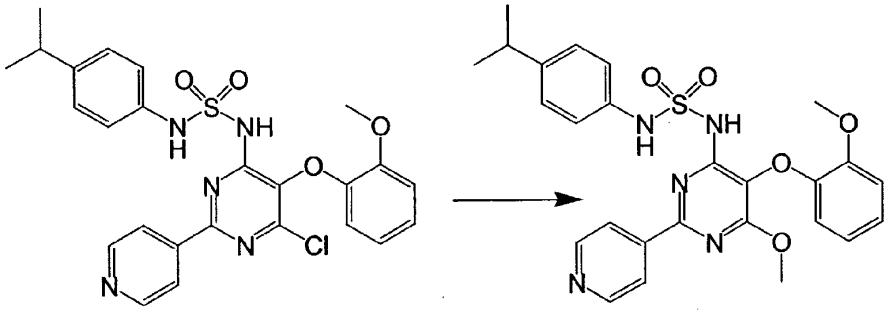
b) The solution prepared as described under a) was then added at 0°C within 1 h to a solution of benzylamine (10.7 g) and triethylamine (15.32 ml) in DCM (200 ml). Stirring was continued for 10 h at rt. The mixture was concentrated in vacuo, taken into EtOAc (500 ml) and washed with water (2 times 40 ml) and brine (30 ml), dried with magnesium sulfate and again concentrated in vacuo. The crude material was crystallized from EtOAc and dried at HV to give ZP1 (13.68 g). ZP1 was dissolved in dioxane (20 ml) and 120 ml 4 M HCl in dioxane was added within 1 h at rt. Stirring was continued for 8 h followed by complete evaporation of the solvents and drying at HV to give benzylsulfamide (9.47 g).

Further –HN-CH_2-aryl/–HN-CH_2-heteroaryl/–HN-CH_2-alkyl/–HN-CH_2-cycloalkyl/–HN-CH_2-heterocyclyl and other sulfamic acid amides (as given by the formulae in ***Figure 2***) can be prepared according to the procedure described in **Referential Example 22.**

Figure 2:

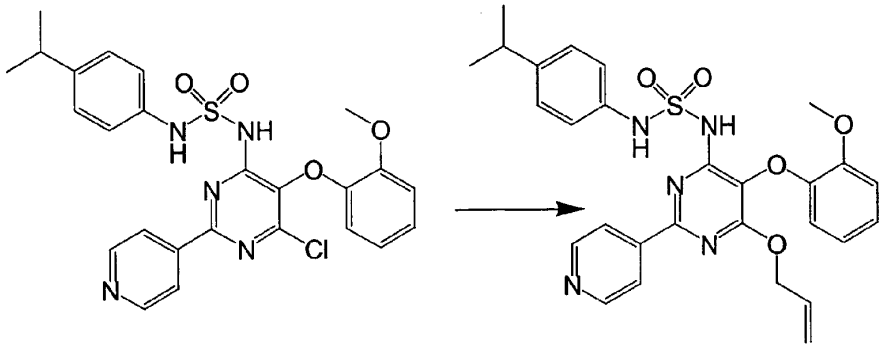


Example 1:



To a mixture of methanol (1 ml) and THF (2 ml) was added sodium hydride (100 mg, 60% dispersion in mineral oil) followed by the addition of 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg, Referential Example 1e)). DMF (0.5 ml) was added and the reaction mixture was heated to 80°C for 20 h. The solvents were evaporated, water (14 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water to give 4-i-propyl-phenyl sulfamic acid-[6-methoxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg). t_R = 5.08 min, (LC); $[M+H]^+$ = 522.45 (ES+).

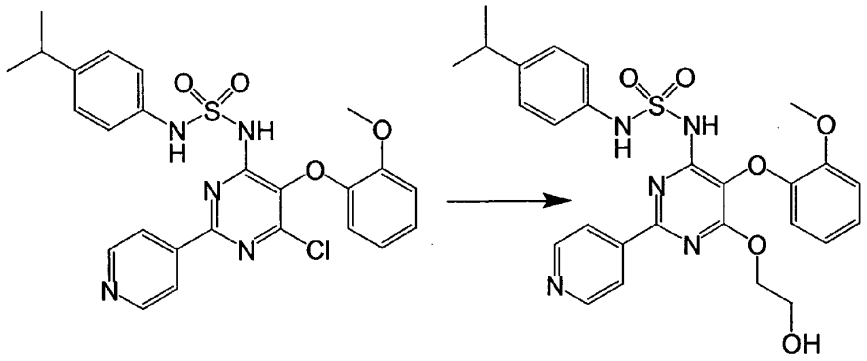
Example 2:



To a mixture of allyl alcohol (1 ml) and THF (2 ml) was added sodium hydride (100 mg, 60% dispersion in mineral oil) followed by the addition of 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (100 mg, Referential Example 1e)). DMF (0.5 ml) was added and the reaction mixture was heated to 80°C for 20 h. The solvents were evaporated, water (14 ml) and a 10% solution of citric acid was added until the pH was 3. The

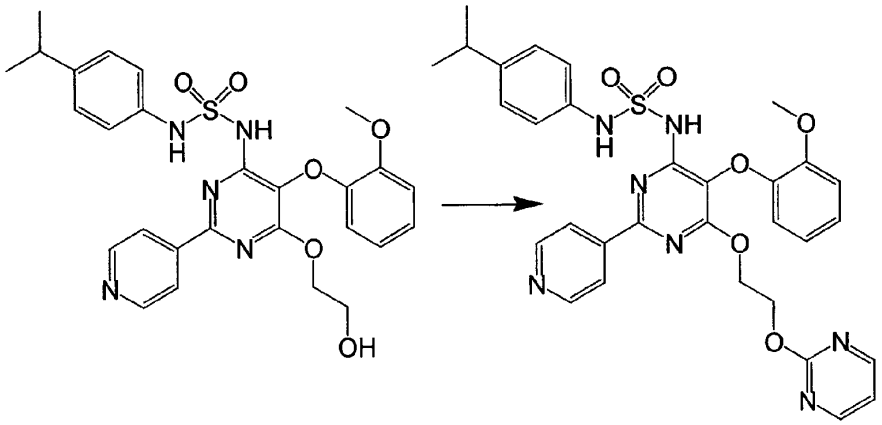
precipitate was filtered off and washed with water and purified by chromatography through silicagel with EtOAc / Hex = 3 : 2 to give 4-i-propyl-phenyl sulfamic acid-[6-allyloxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg). t_R = 5.36 min, (LC); $[M+H]^+$ = 548.46 (ES+).

Example 3:



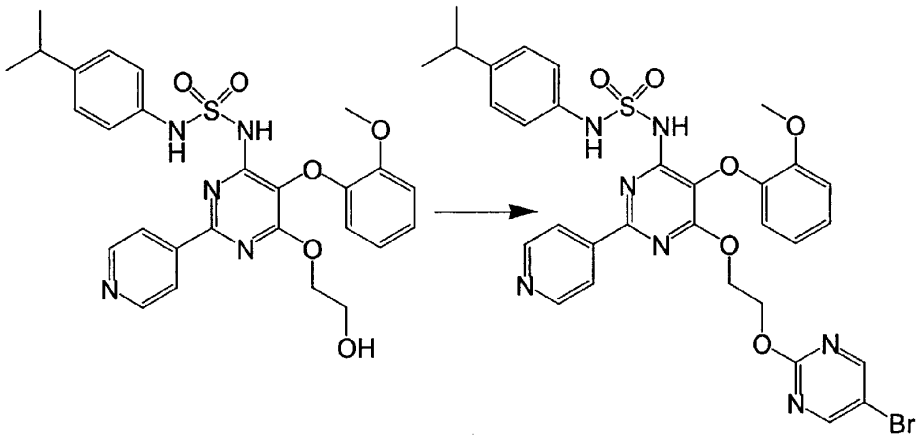
Sodium hydride (17 mg, 60% dispersion in mineral oil) was added to ethylene glycol (1.2 ml) followed by addition of dimethoxyethane (0.5 ml). Stirring was continued for 30 min, then 4-i-propyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (45 mg, Referential Example 1e)) was added and the reaction mixture was heated to 80°C for 48 h. The solvents were evaporated, water (10 ml) and a 10% solution of citric acid was added until the pH was 3 followed by extraction with EtOAc. The organic layers were dried over sodium sulfate and the solvent was evaporated. The crude product was purified by chromatography through silicagel with EtOAc to give 4-i-propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (38 mg). t_R = 4.56 min, (LC); $[M+H]^+$ = 552.36 (ES+).

Example 4:



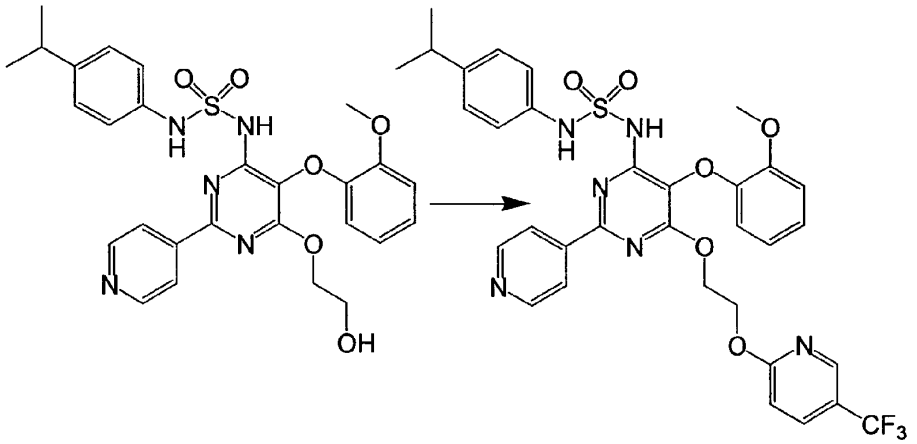
4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (60 mg, Example 3) was dissolved in THF (8 ml) and sodium hydride (14 mg, 60% dispersion in mineral oil) was added and stirring continued for 10 min. 2-Chloro-pyrimidine (22 mg) was added and the mixture was heated to 60°C for 90 min. DMF (0.5 ml) was added and the solution was stirred at r.t. for 48 h. The solvents were evaporated, water (12 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water and purified by recrystallization from diethyl ether to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(pyrimidin-2-yloxy)-ethoxy]-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (50 mg). t_R = 4.80 min, (LC); $[M+H]^+$ = 630.91 (ES+).

Example 5:



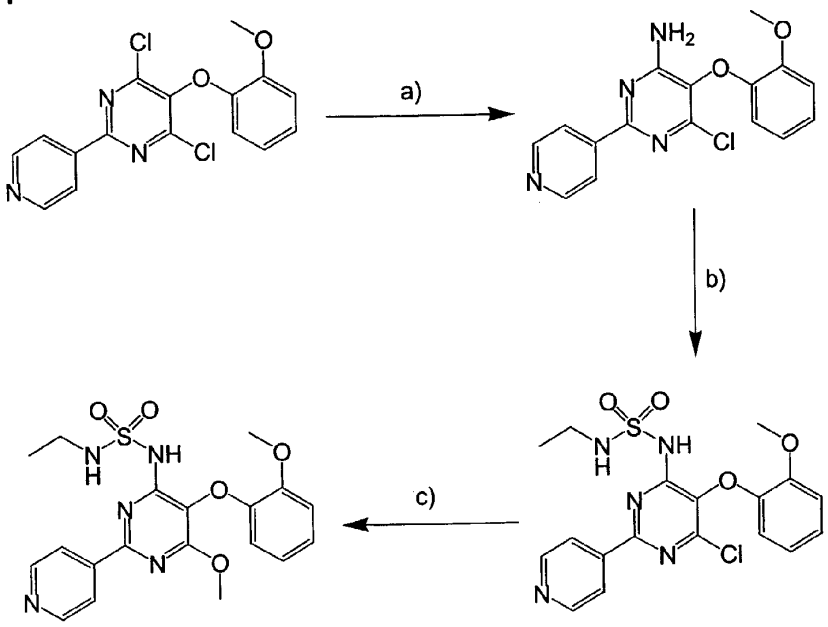
4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (60 mg, Example 3) was dissoved in THF (8 ml). Sodium hydride (14 mg, 60% dispersion in mineral oil) was added and stirring continued for 10 min. 5-Bromo-2-chloro-pyrimidine (37 mg) was added and the mixture was heated to 60°C for 120 min. DMF (0.5 ml) was added and the solution was stirred at r.t. for 48 h. The solvents were evaporated, water (12 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off and washed with water and purified by chromatography through silica gel with EtOAc / Hex = 1 : 1 to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (55.4 mg). t_R = 5.30 min, (LC); $[M+H]^+$ = 710.35 (ES+).

Example 6:



4-i-Propyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (50 mg, Example 3) was dissolved in THF (8 ml). Sodium hydride (12 mg, 60% dispersion in mineral oil) was added and stirring continued for 10 min. 5-Trifluoromethyl-2-chloro-pyridine (28 mg) was added and the mixture was heated to 60°C for 180 min. The solvents were evaporated, water (12 ml) and a 10% solution of citric acid was added until the pH was 3. The precipitate was filtered off, washed with water and purified by recrystallization with diethylether to give 4-i-propyl-phenyl sulfamic acid-[6-[2-(5-trifluoromethyl-pyridin-2-yloxy)-ethoxy]-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (41 mg). t_R = 5.81 min, (LC); $[M+H]^+$ = 697.17 (ES+).

Example 7:



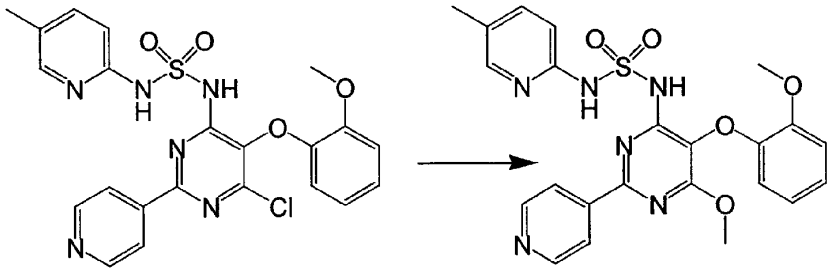
a) 4,6-Dichloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (2.9 g, Referential Example 1d)) was suspended in dioxane (30 ml) and ammonia (gaseous) was introduced until the solution was saturated. Stirring was continued for 7 days while the saturation of the reaction mixture with ammonia (gaseous) was repeated every 16 to 20 h. The solvent was evaporated, water was added to the residue and the precipitate was filtered off. After drying at HV / 50°C 4-amino-6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (2.7 g) was obtained.

b) 4-Amino-6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-pyrimidine (100 mg) was dissolved in THF (5 ml) and DCM (5 ml). DBU (46 mg) and DMAP (37 mg) were added followed by the addition of ethyl-sulfamoylchloride (prepared from ethylamine hydrochloride and sulfuryl chloride). The mixture was stirred for 12 h at r.t.. The solvent was evaporated . Water and a 10% solution of citric acid were added followed by extraction with EtOAc and DCM. The combined organic layers were dried over sodium sulfate and the solvent was evaporated under reduced pressure. After purification of the residue by chromatography over silicagel with EtOAc / methanol / ammonia = 4 : 1 : 0.5, ethyl sulfamic acid-[6-chloro-5-(o-

methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg) was obtained. t_R = 4.31 min, (LC); $[M+H]^+$ = 436.14 (ES+).

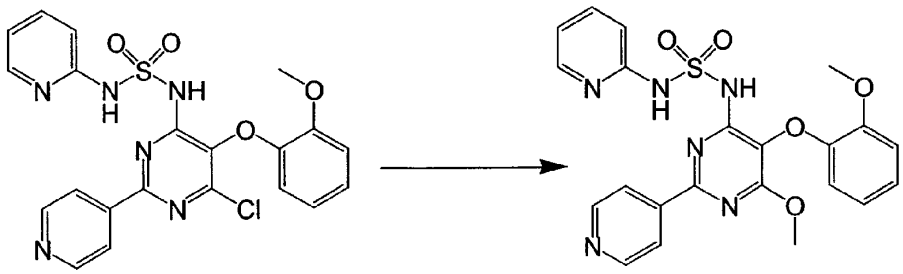
c) Ethyl sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (14 mg) was suspended in methanol (1 ml) followed by addition of a solution of potassium tert.-butylate (8.5 mg) in methanol (1 ml). The mixture was heated to 85°C for 18 h. The solvent was evaporated and water and a 10% solution of citric acid was added. The precipitate was filtered off and washed with water. After drying at HV ethyl sulfamic acid-[6-methoxy-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-pyrimidin-4-yl]-amide (10 mg) were obtained. t_R = 4.25 min, (LC); $[M+H]^+$ = 432.32 (ES+).

Example 8:



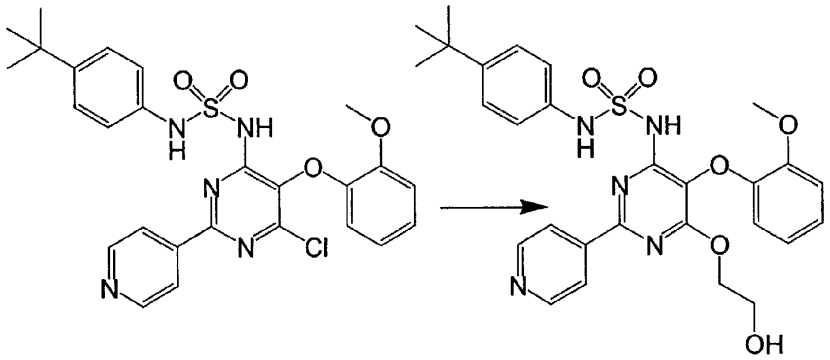
Sodium hydride (100 mg, 60% dispersion in mineral oil) was dissloved in methanol (1.2 ml). 5-methyl-pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (50 mg, Referential Example 11), DMF (0.5 ml) and THF (1 ml) was added and the solution was stirred for 30 h at 80°C. The solvents were evaporated and the residue was washed with hexane (3x) and the hexane was decanted. A solution of 10% citric acid was added and the precipitate was filtered off and washed with water. After drying at HV 5-methyl-pyridine-2-sulfamic acid-[6-methoxy-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (37 mg) was obtained. t_R = 3.73 min, (LC); $[M+H]^+$ = 495.38 (ES+).

Example 9:



Pyridine-2-sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (15 mg, Referential Example 12) was suspended in THF (1 ml) and DMF (0.2 ml) and sodium methylate (40 mg) was added. The mixture was stirred for 90 h at 80°C followed by evaporation of the solvents. A solution of 10% citiric acid was added to the residue. The precipitate was filtered off and washed with water. After drying at HV pyridine-2-sulfamic acid-[6-methoxy-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (7 mg) was obtained. t_R = 3.55 min, (LC); $[M-H]^+$ = 479.41 (ES-).

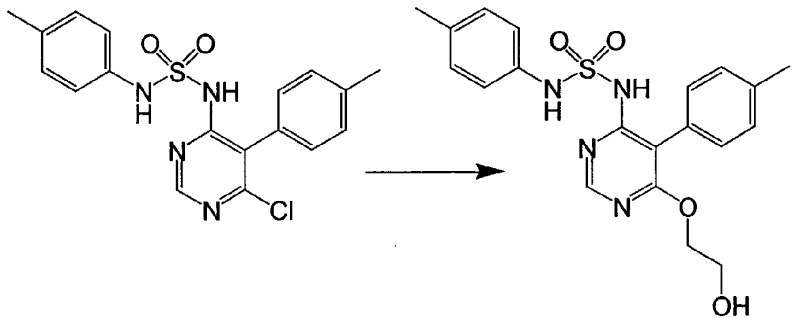
Example 10:



Sodium hydride (28 mg, 60% dispersion in mineral oil) was dissolved in ethyleneglycol (1.2 ml) and 1,2-dimethoxyethane (1 ml). 4-t-butyl-phenyl sulfamic acid-[6-chloro-5-(o-methoxyphenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (75 mg, Referential Example 10) was added and stirring continued for 90 h at 80°C. The mixture was evaporated and a 10% solution of citric acid was added. The precipitate was filtered off and washed with water. After purification by

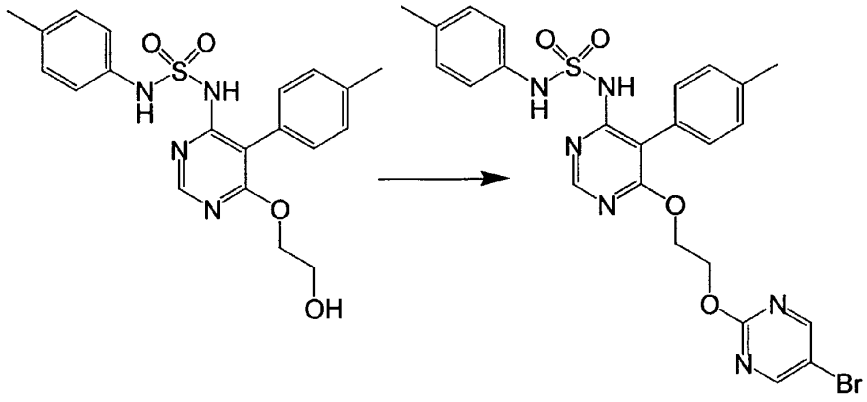
chromatography over silica gel with EtOAc 4-t-butyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(o-methoxy-phenoxy)-2-(4-pyridyl)-4-pyrimidinyl]-amide (40 mg) could be isolated. t_R = 4.81 min, (LC); $[M+H]^+$ = 566.35 (ES-).

Example 11:



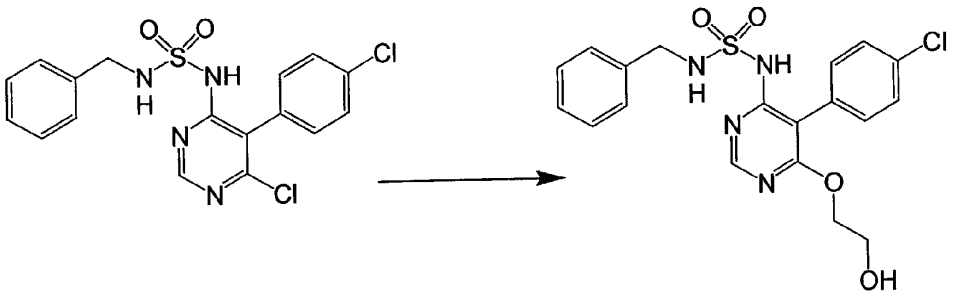
To a mixture of 1,2-dimethoxyethan (15 ml) and ethyleneglycol (40 ml) was added sodium (298 mg) in small portions. The mixture was stirred until the sodium was completely dissolved. Then DMF (15 ml), followed by 4-methyl-phenyl sulfamic acid-[6-chloro-5-(p-tolyl)-4-pyrimidinyl]-amide (1.0 g, Referential Example 14) was added. Stirring was continued for 4 days at 100°C. The mixture was evaporated and water (150 ml) was added to the residue followed by addition of acetic acid (1.0 ml). The precipitate was filtered off, washed with water and dried. The crude material was purified by chromatography over silicagel with EtOAc / methanol / aqueous ammonia (25%) = 4 / 1 / 0.5 to give 4-methyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(p-tolyl)-4-pyrimidinyl]-amide (500 mg). t_R = 4.38 (LC); $[M+H]^+$ = 415.19 (ES+).

Example 12:



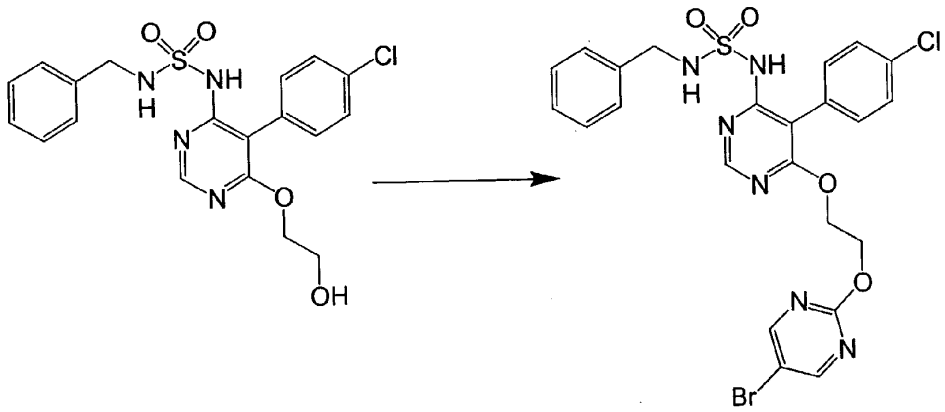
To 4-methyl-phenyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(p-tolyl)-4-pyrimidinyl]-amide (47 mg, Example 11) dissolved in THF (8 ml) was added sodium hydride (14.6 mg, 60% dispersion in mineral oil) and stirring was continued for 15 min followed by the addition of 5-bromo-2-chloro-pyrimidine (39 mg). Stirring was continued for 2 h at 50°C and 80 h at r.t.. The mixture was evaoprated and a 10% citric acid solution was added. The precipitate was filtered off, washed with water and purified by chromatography over silicagel with EtOAc / Hex = 1 / 1 to give 4-methyl-phenyl sulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(p-tolyl)-4-pyrimidinyl]-amide (34 mg). t_R = 5.34 (LC); $[M+H]^+$ = 573.02 (ES+).

Example 13:



Potassium tert.-butoxide (3.5 g) was dissolved in ethyleneglycol (35 ml), benzyl sulfamic acid-[6-chloro-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (1.8 g, Referential Example 15) was added and the mixture was heated to 102°C for 11 h. The mixture was poured onto ice/water and acidified to pH = 4 with solid citric acid. The precipitated product was filtered off, washed with water and dried at HV to give benzyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (1.77 g). t_R = 4.36 (LC); $[M+H]^+$ = 435.09 (ES+).

Example 14:



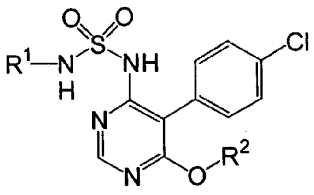
Benzyl sulfamic acid-[6-(2-hydroxy-ethoxy)-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (375 mg, Example 13) was dissolved in THF (30 ml) followed by addition of sodium hydride (60 % dispersion in mineral oil) (140 mg).

The mixture was stirred for 30 min followed by the addition of 5-bromo-2-chloro-pyrimidine (320 mg). Stirring was continued at 60°C for 8 h. The reaction mixture was poured onto ice/water and acidified with solid citric acid. The precipitate was filtered off and purified by chromatography over silicagel with hexane / EtOAc = 2/1 to give benzyl sulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-amide (198 mg). t_R = 5.32 (LC); $[M+H]^+$ = 592.68 (ES+).

Examples 15 - 202:

The corresponding starting materials are treated in a manner according to the procedures given in examples 1 – 14 to give the compounds as listed in Tables 3 - 36.

Table 3:



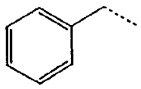
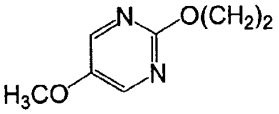
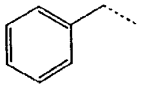
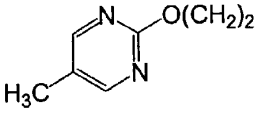
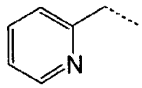
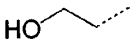
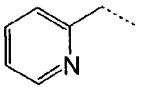
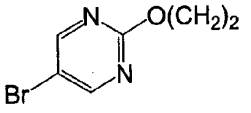
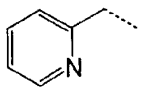
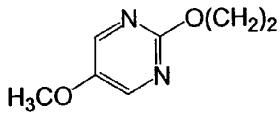
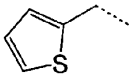
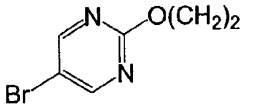
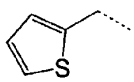
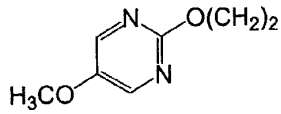
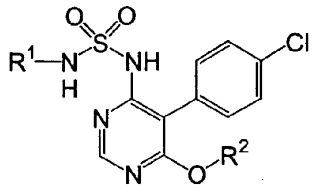
Ex. No.	R^1	R^2	LC-MS
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16			t_R = 4.95 $[M+H]^+$: 527.28
17			t_R = 3.28 $[M+H]^+$: 435.65
18			t_R = 4.46 $[M+H]^+$: 594.25
19			t_R = 4.03 $[M+H]^+$: 544.10
20			t_R = 5.21 $[M+H]^+$: 599.20
21			t_R = 4.84 $[M+H]^+$: 548.97

Table 4:



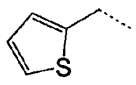
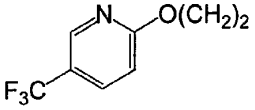
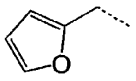
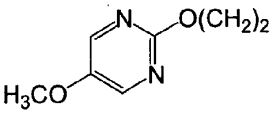
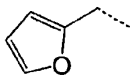
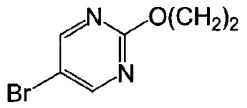
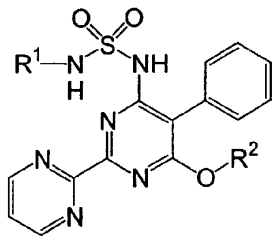
Ex. No.	R^1	R^2	LC-MS
22			t_R = 5.67 $[M+H]^+$: 585.75
23			t_R = 4.67 $[M+H]^+$: 532.77
24			t_R = 5.07 $[M+H]^+$: 582.71

Table 5:



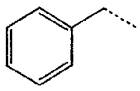
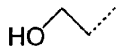
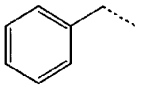
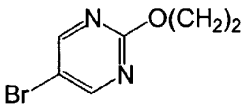
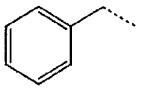
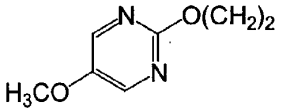
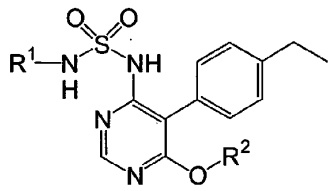
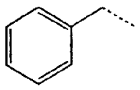
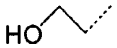
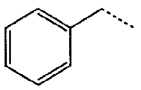
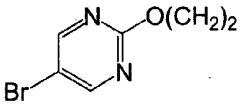
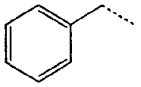
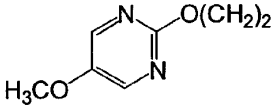
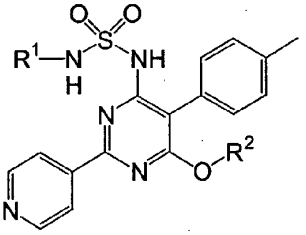
Ex. No.	R^1	R^2	LC-MS
25			t_R = 4.07 $[M+H]^+$: 479.11
26			t_R = 4.88 $[M+H]^+$: 637.54
27			t_R = 4.51 $[M-H]^+$: 584.93

Table 6:



Ex. No.	R^1	R^2	LC-MS
28			t_R = 4.52 $[M+H]^+$: 429.14
29			t_R = 5.48 $[M+H]^+$: 585.38
30			t_R = 5.12 $[M+H]^+$: 537.22



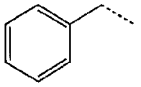
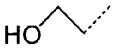
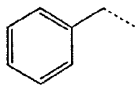
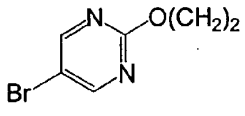
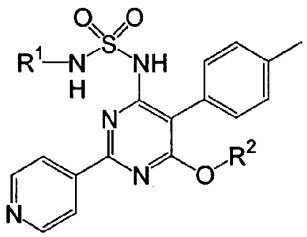
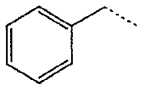
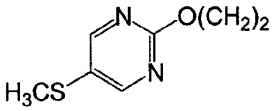
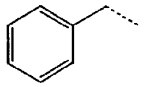
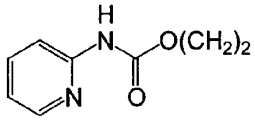
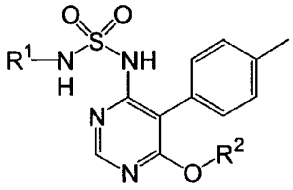
31			t_R = 3.99 $[M+H]^+$: 492.23
32			t_R = 5.04 $[M+H]^+$: 650.50

Table 7:



Ex. No.	R^1	R^2	LC-MS
33			t_R = 5.00 $[M+H]^+$: 616.18
34			t_R = 4.47 $[M+H]^+$: 612.41



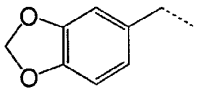
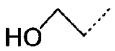
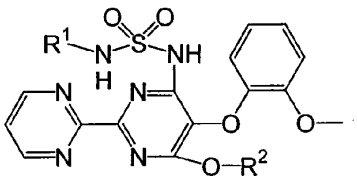
35			t_R = 4.27 $[M+H]^+$: 459.15

Table 8:



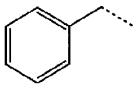
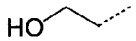
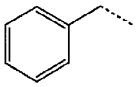
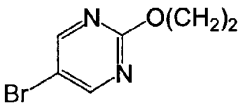
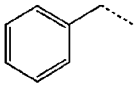
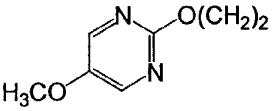
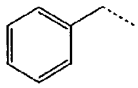
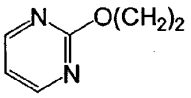
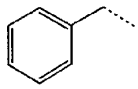
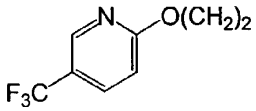
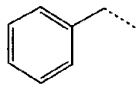
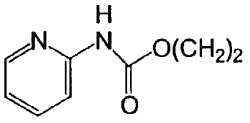
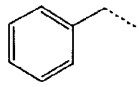
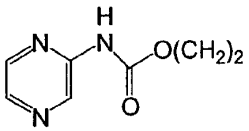
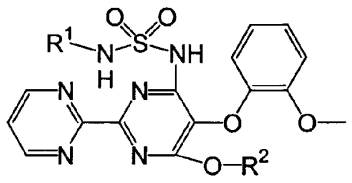
Ex. No.	R^1	R^2	LC-MS
36			t_R = 4.13 $[M+H]^+$: 525.17
37			t_R = 4.87 $[M+H]^+$: 682.50
38			t_R = 4.55 $[M+H]^+$: 631.05
39			t_R = 4.38 $[M+H]^+$: 603.45
40			t_R = 5.31 $[M+H]^+$: 670.27
41			t_R = 4.36 $[M+H]^+$: 645.11
42			t_R = 4.29 $[M+H]^+$: 646.12

Table 9:



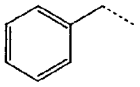
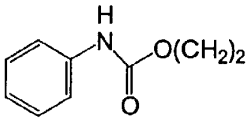
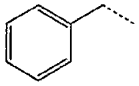
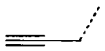
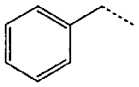
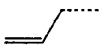
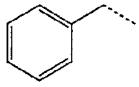
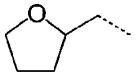
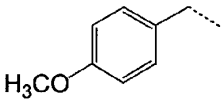
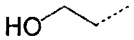
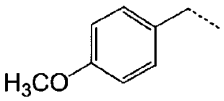
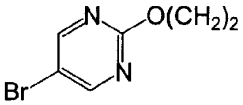
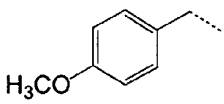
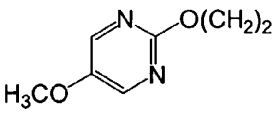
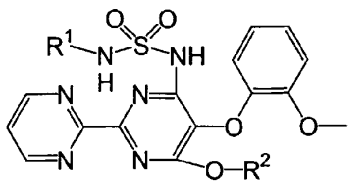
Ex. No.	R^1	R^2	LC-MS
43			t_R = 4.89 $[M+H]^+$: 644.24
44			t_R = 4.60 $[M+H]^+$: 519.18
45			t_R = 4.74 $[M+H]^+$: 521.21
46			t_R = 4.71 $[M+H]^+$: 565.66
47			t_R = 4.10 $[M+H]^+$: 555.59
48			t_R = 4.82 $[M+H]^+$: 713.18
49			t_R = 4.52 $[M+H]^+$: 663.54

Table 10:



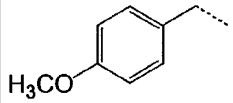
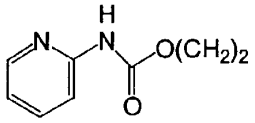
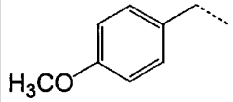
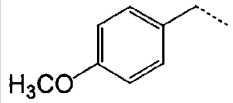
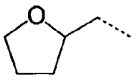
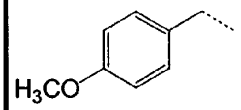
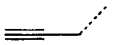
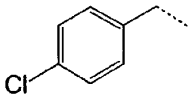
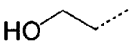
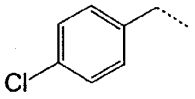
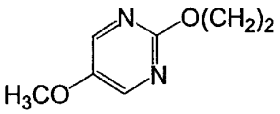
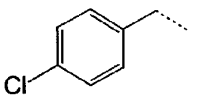
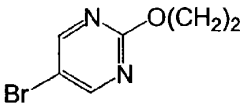
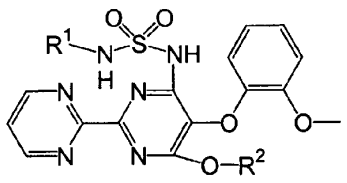
Ex. No.	R^1	R^2	LC-MS
50			t_R = 4.32 $[M+H]^+$: 675.34
51			t_R = 4.51 $[M+H]^+$: 524.91
52			t_R = 4.67 $[M+H]^+$: 595.20
53			t_R = 4.65 $[M+H]^+$: 549.33
54			t_R = 4.35 $[M+H]^+$: 559.30
55			t_R = 4.79 $[M+H]^+$: 667.34
56			t_R = 5.11 $[M+H]^+$: 717.09

Table 11:



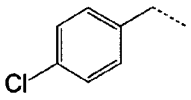
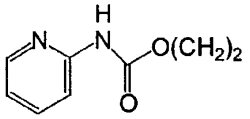
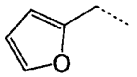
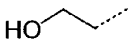
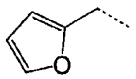
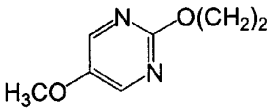
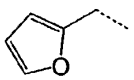
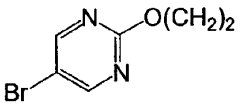
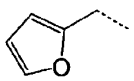
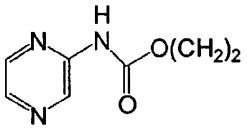
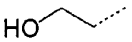
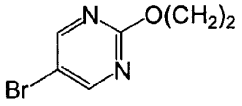
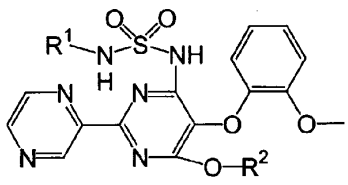
Ex. No.	R^1	R^2	LC-MS
57			t_R =4.71 $[M-H]^+$: 678.68
58			t_R = 3.93 $[M+H]^+$: 515.38
59			t_R = 4.46 $[M+H]^+$: 623.48
60			t_R = 4.75 $[M+H]^+$: 673.39
61			t_R = 4.15 $[M+H]^+$: 636.34
183			t_R = 3.72 $[M+H]^+$: 462.98
184			t_R = 4.54 $[M+H]^+$: 619.06

Table 12:



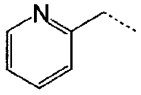
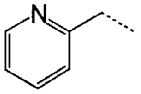
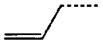
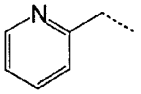
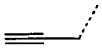
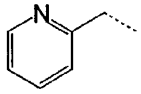
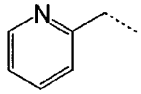
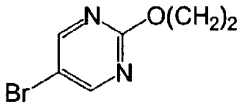
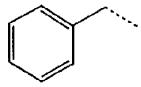
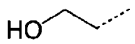
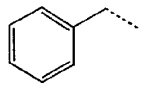
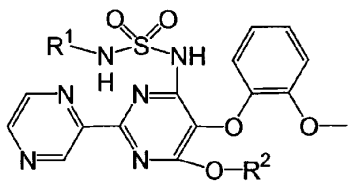
Ex. No.	R^1	R^2	LC-MS
62			t_R = 3.38 $[M+H]^+$: 526.04
63			t_R = 4.29 $[M+H]^+$: 521.79
64			t_R = 4.10 $[M+H]^+$: 520.10
65			t_R = 3.87 $[M+H]^+$: 496.09
66			t_R = 4.40 $[M+H]^+$: 683.15
67			t_R = 4.30 $[M+H]^+$: 525.25
68			t_R = 4.84 $[M-H]^+$: 493.13

Table 13:



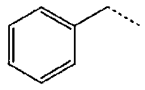
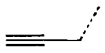
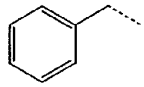
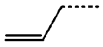
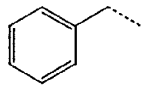
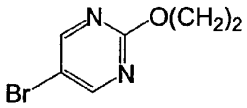
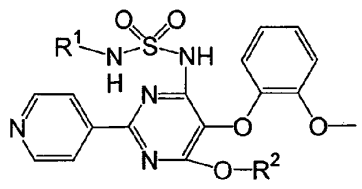
Ex. No.	R^1	R^2	LC-MS
69			t_R = 4.95 $[M-H]^+$: 517.58
70			t_R = 5.13 $[M+H]^+$: 521.30
71			t_R = 5.22 $[M+H]^+$: 683.42

Table 14:



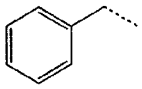
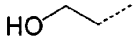
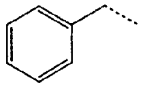
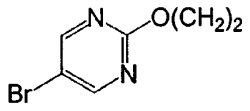
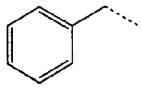
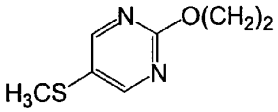
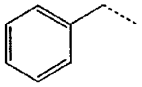
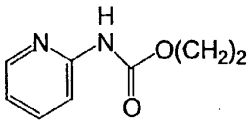
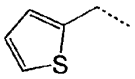
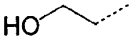
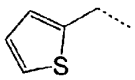
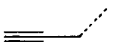
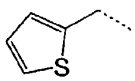
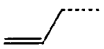
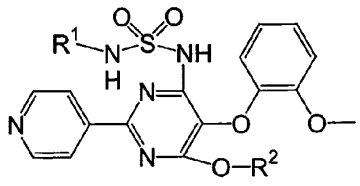
Ex. No.	R^1	R^2	LC-MS
72			t_R = 3.79 $[M+H]^+$: 524.28
73			t_R = 4.76 $[M+H]^+$: 681.59
74			t_R = 4.70 $[M+H]^+$: 648.25
75			t_R = 4.30 $[M+H]^+$: 645.65
76			t_R = 3.73 $[M+H]^+$: 530.25
77			t_R = 4.38 $[M+H]^+$: 524.23
78			t_R = 4.59 $[M+H]^+$: 526.10

Table 15:



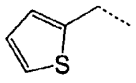
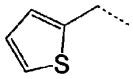
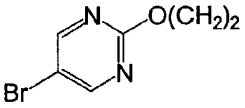
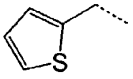
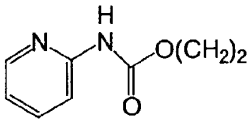
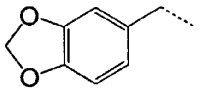
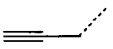
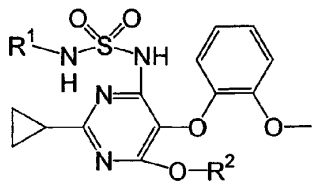
Ex. No.	R^1	R^2	LC-MS
79			t_R = 4.36 $[M+H]^+$: 500.14
80			t_R = 4.82 $[M+H]^+$: 688.54
81			t_R = 4.25 $[M+H]^+$: 650.09
82			t_R = 4.43 $[M+H]^+$: 562.16

Table 16:



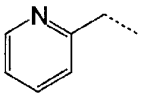
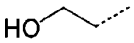
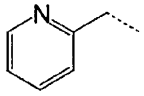
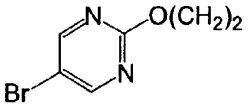
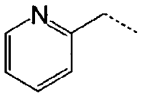
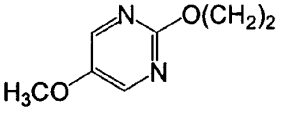
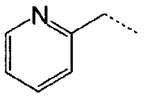
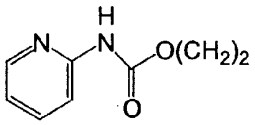
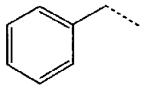
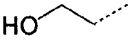
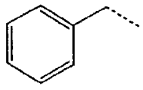
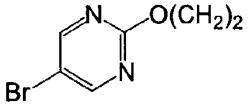
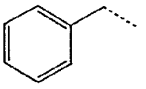
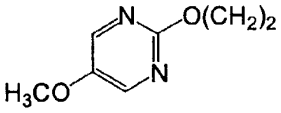
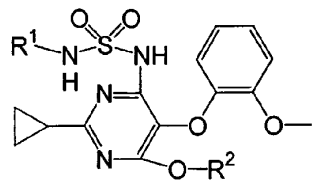
Ex. No.	R^1	R^2	LC-MS
83			t_R = 3.38 $[M+H]^+$: 488.30
84			t_R = 4.46 $[M+H]^+$: 646.17
85			t_R = 4.15 $[M+H]^+$: 596.31
86			t_R = 3.96 $[M+H]^+$: 608.69
87			t_R = 4.77 $[M+H]^+$: 488.18
88			t_R = 5.89 $[M+H]^+$: 644.83
89			t_R = 5.56 $[M+H]^+$: 595.20

Table 17:



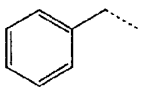
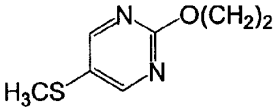
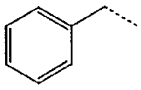
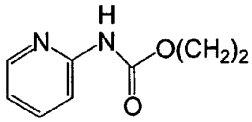
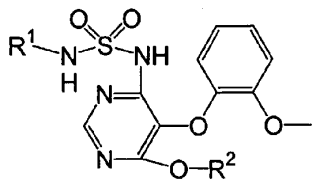
Ex. No.	R^1	R^2	LC-MS
90			t_R = 5.82 $[M+H]^+$: 611.19
91			t_R = 5.31 $[M+H]^+$: 607.32

Table 18:



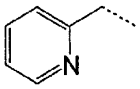
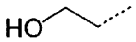
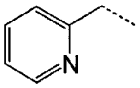
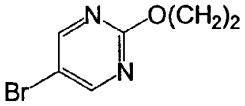
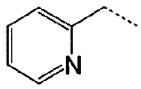
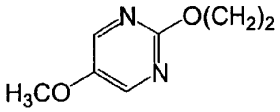
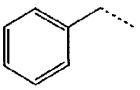
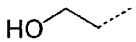
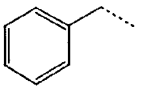
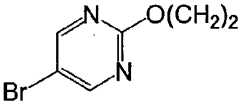
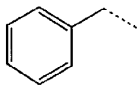
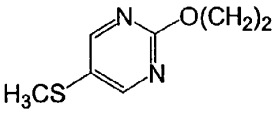
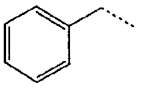
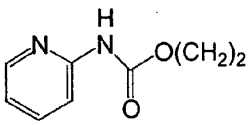
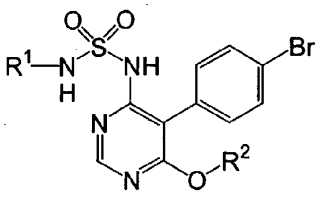
Ex. No.	R^1	R^2	LC-MS
92			t_R = 2.54 $[M+H]^+$: 448.08
93			t_R = 4.20 $[M+H]^+$: 605.54
94			t_R = 3.82 $[M+H]^+$: 556.15
95			t_R = 4.14 $[M+H]^+$: 447.26
96			t_R = 5.10 $[M+H]^+$: 604.67
97			t_R = 5.01 $[M+H]^+$: 571.18
98			t_R = 4.53 $[M+H]^+$: 567.23

Table 19:



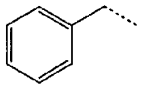
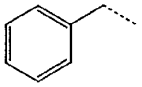
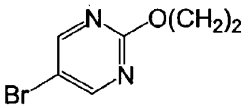
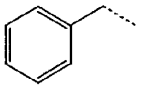
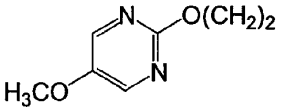
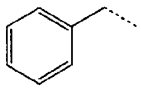
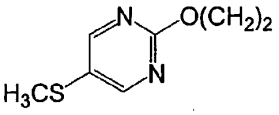
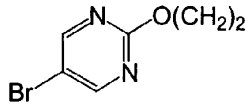
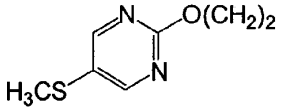
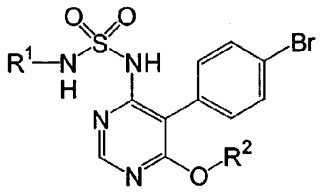
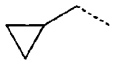
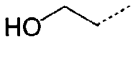
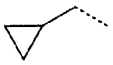
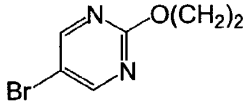
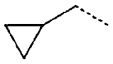
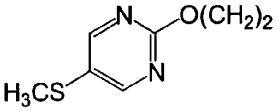
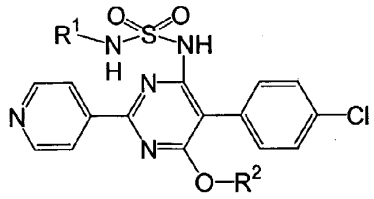
Ex. No.	R^1	R^2	LC-MS
99			t_R = 4.46 $[M+H]^+$: 481.20
100			t_R = 5.55 $[M+H]^+$: 637.07
101			t_R = 5.14 $[M+H]^+$: 589.15
102			t_R = 5.55 $[M+H]^+$: 603.27
103			t_R = 3.88 $[M+H]^+$: 419.01
104			t_R = 4.93 $[M+H]^+$: 575.13
105			t_R = 4.84 $[M+H]^+$: 543.20

Table 20:



Ex. No.	R^1	R^2	LC-MS
106			t_R = 4.12 $[M+H]^+$: 445.11
107			t_R = 5.03 $[M+H]^+$: 601.28
108			t_R = 4.98 $[M+H]^+$: 568.44



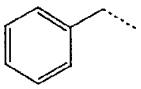
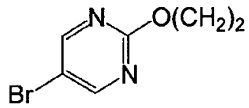
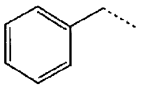
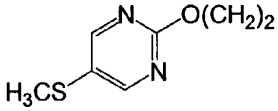
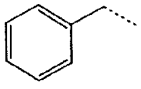
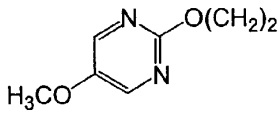
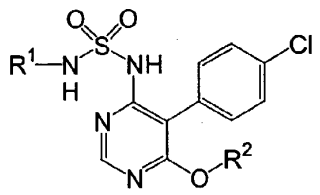
109			t_R = 4.92 $[M+H]^+$: 670.30
110			t_R = 5.07 $[M+H]^+$: 636.34
111			t_R = 4.76 $[M+H]^+$: 620.07

Table 21:



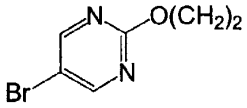
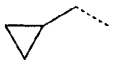
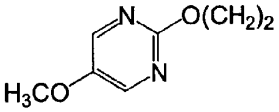
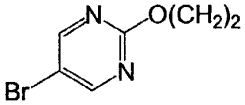
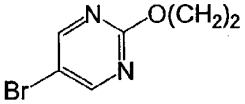
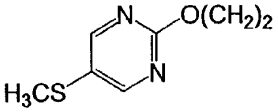
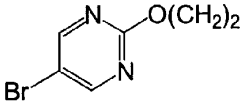
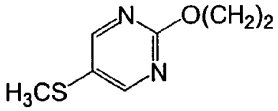
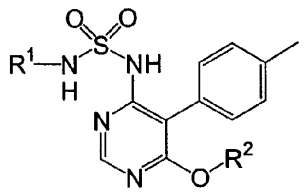
Ex. No.	R^1	R^2	LC-MS
112			t_R = 5.28 $[M+H]^+$: 557.18
113			t_R = 4.86 $[M+H]^+$: 507.28
114			t_R = 4.92 $[M+H]^+$: 543.16
115			t_R = 4.87 $[M+H]^+$: 531.13
116			t_R = 4.78 $[M+H]^+$: 497.24
117			t_R = 5.32 $[M+H]^+$: 559.19
118			t_R = 5.23 $[M+H]^+$: 525.31

Table 22:



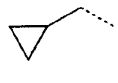
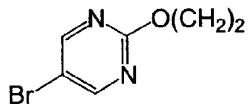
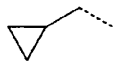
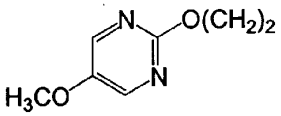
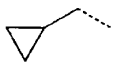
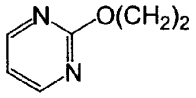
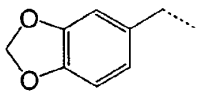
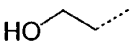
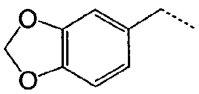
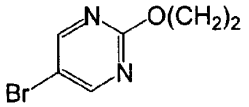
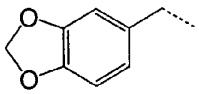
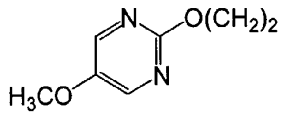
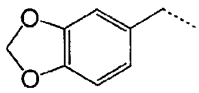
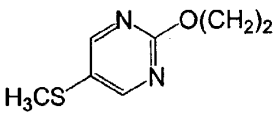
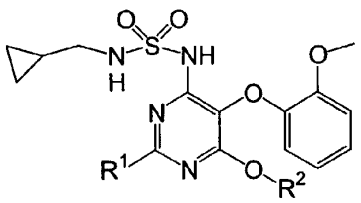
Ex. No.	R^1	R^2	LC-MS
119			t_R = 5.20 $[M+H]^+$: 537.14
120			t_R = 4.77 $[M+H]^+$: 487.25
121			t_R = 4.56 $[M+H]^+$: 456.89
144			t_R = 4.27 $[M+H]^+$: 459.15
145			t_R = 5.77 $[M+H]^+$: 616.66
146			t_R = 6.01 $[M+H]^+$: 567.36
147			t_R = 5.22 $[M+H]^+$: 582.88

Table 23:



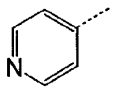
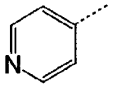
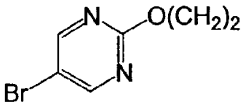
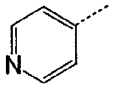
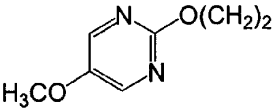
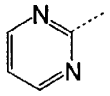
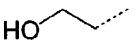
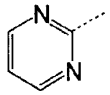
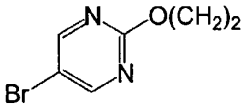
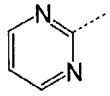
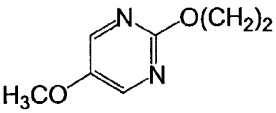
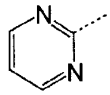
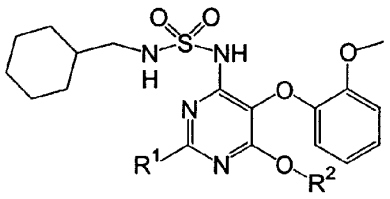
Ex. No.	R^1	R^2	LC-MS
122			t_R = 3.63 $[M+H]^+$: 488.49
123			t_R = 4.66 $[M+H]^+$: 646.30
124			t_R = 4.29 $[M+H]^+$: 596.44
125			t_R = 3.96 $[M+H]^+$: 489.56
126			t_R = 4.79 $[M+H]^+$: 645.07
127			t_R = 4.47 $[M+H]^+$: 597.31
128			t_R = 4.47 $[M+H]^+$: 483.34

Table 24:



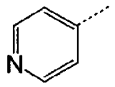
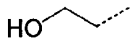
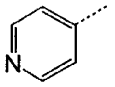
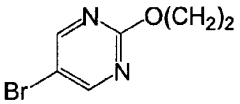
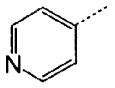
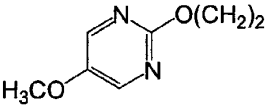
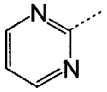
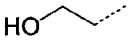
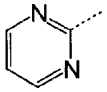
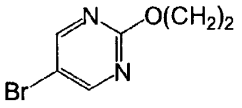
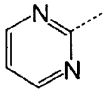
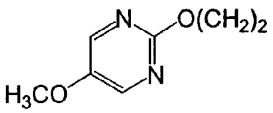
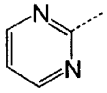
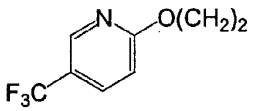
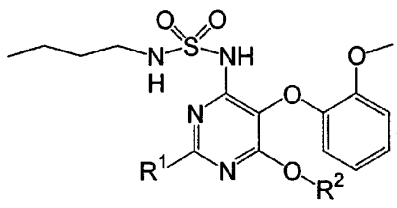
Ex. No.	R^1	R^2	LC-MS
129			t_R = 4.29 $[M+H]^+$: 530.49
130			t_R = 5.35 $[M+H]^+$: 688.27
131			t_R = 4.93 $[M+H]^+$: 638.64
132			t_R = 4.70 $[M+H]^+$: 531.54
133			t_R = 5.39 $[M+H]^+$: 689.26
134			t_R = 5.06 $[M+H]^+$: 639.36
135			t_R = 5.83 $[M+H]^+$: 676.34

Table 25:



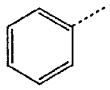
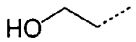
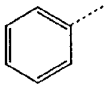
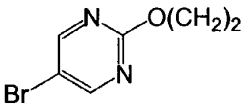
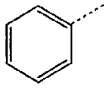
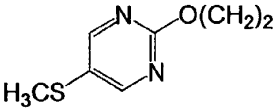
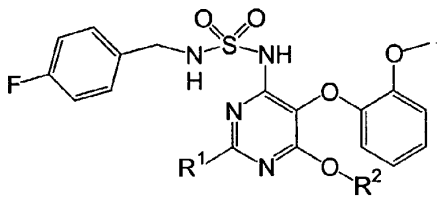
Ex. No.	R^1	R^2	LC-MS
136			t_R = 4.11 $[M+H]^+$: 491.29
137			t_R = 4.88 $[M+H]^+$: 649.18
138			t_R = 4.82 $[M+H]^+$: 615.67

Table 26:



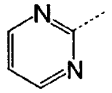
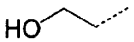
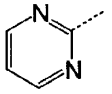
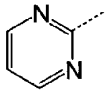
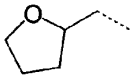
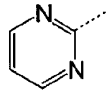
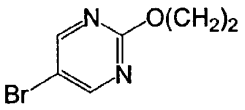
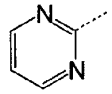
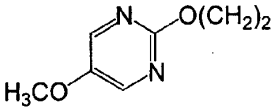
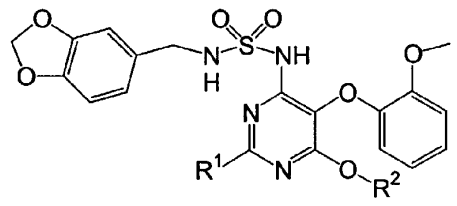
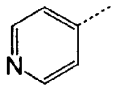
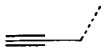
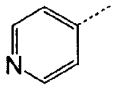
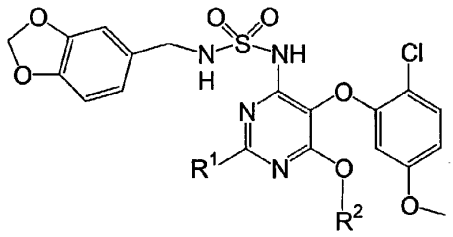
Ex. No.	R^1	R^2	LC-MS
139			t_R = 4.27 $[M+H]^+$: 543.37
140			t_R = 4.55 $[M+H]^+$: 513.31
141			t_R = 4.70 $[M+H]^+$: 583.52
142			t_R = 4.92 $[M+H]^+$: 701.37
143			t_R = 4.60 $[M+H]^+$: 651.40

Table 27:



Ex. No.	R^1	R^2	LC-MS
148			t_R = 4.43 $[M+H]^+$: 562.16
149		H_3C----	t_R = 4.27 $[M+H]^+$: 538.18



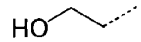
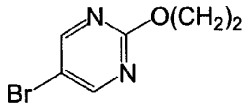
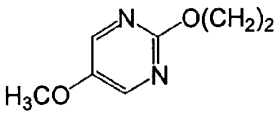
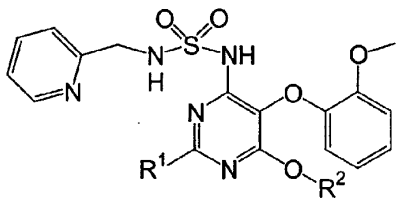
150	H----		t_R = 4.37 $[M-H]^+$: 522.83
151	H----		t_R = 5.21 $[M+H]^+$: 682.98
152	H----		t_R = 4.86 $[M-H]^+$: 631.19

Table 28:



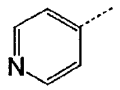
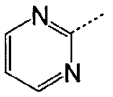
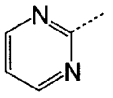
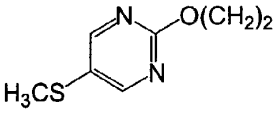
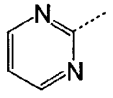
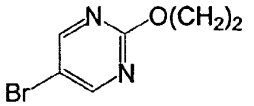
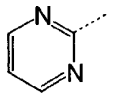
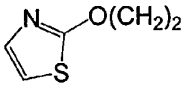
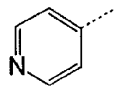
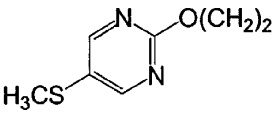
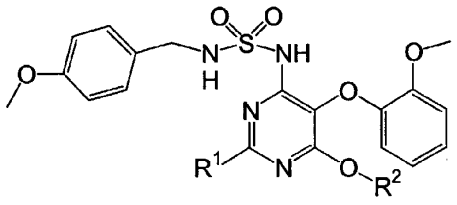
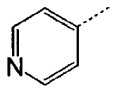
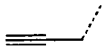
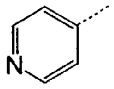
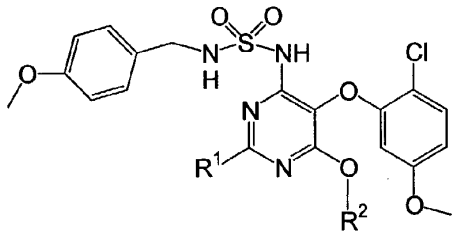
Ex. No.	R^1	R^2	LC-MS
153			t_R = 3.15 $[M-H]^+$: 523.09
154			t_R = 3.20 $[M+H]^+$: 526.44
155			t_R = 3.96 $[M+H]^+$: 650.39
156			t_R = 4.00 $[M+H]^+$: 684.29
157			t_R = 3.86 $[M+H]^+$: 609.32
158			t_R = 4.14 $[M+H]^+$: 649.30

Table 29:



Ex. No.	R^1	R^2	LC-MS
160			t_R = 4.58 $[M+H]^+$: 548.41
161		H_3C·····	t_R = 4.32 $[M+H]^+$: 524.19



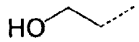
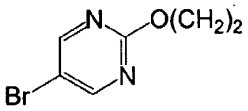
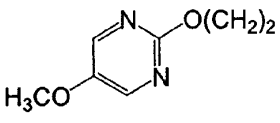
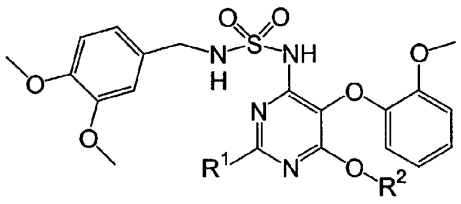
162	H·····		t_R =4.41 $[M+H]^+$: 511.11
163	H·····		t_R = 5.26 $[M+H]^+$: 668.91
164	H·····		t_R = 4.98 $[M+H]^+$: 619.17

Table 30:



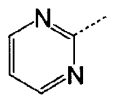
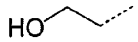
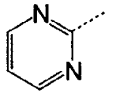
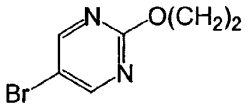
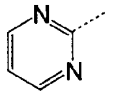
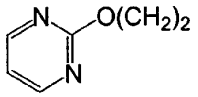
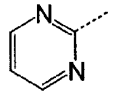
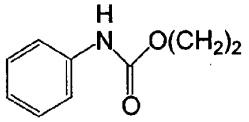
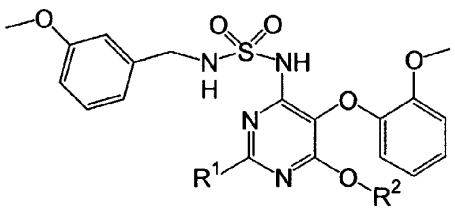
Ex. No.	R^1	R^2	LC-MS
165			t_R = 3.90 $[M+H]^+$: 585.52
166			t_R = 4.69 $[M+H]^+$: 743.19
167			t_R = 4.24 $[M+H]^+$: 663.47
168			t_R = 4.78 $[M+H]^+$: 704.54

Table 31:



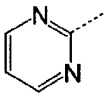
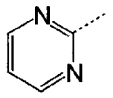
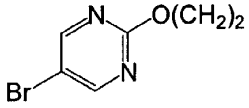
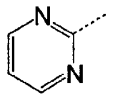
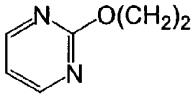
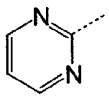
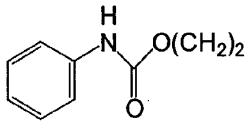
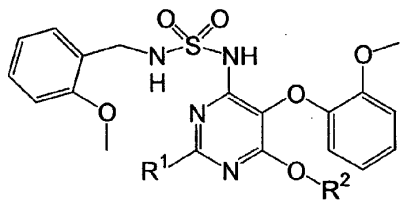
Ex. No.	R^1	R^2	LC-MS
169			t_R = 4.16 $[M+H]^+$: 555.69
170			t_R = 4.76 $[M+H]^+$: 713.26
171			t_R = 4.45 $[M+H]^+$: 633.64
172			t_R = 4.98 $[M+H]^+$: 674.55

Table 32:



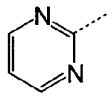
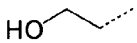
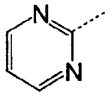
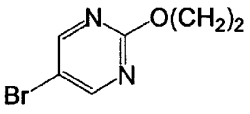
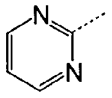
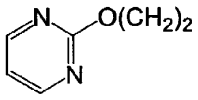
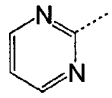
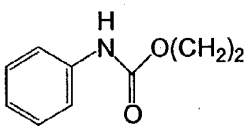
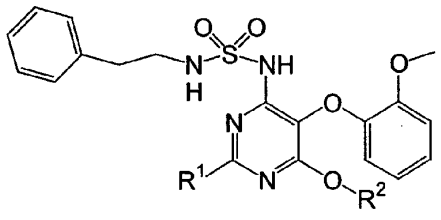
Ex. No.	R^1	R^2	LC-MS
173			t_R = 4.20 $[M+H]^+$: 555.37
174			t_R = 4.99 $[M+H]^+$: 713.35
175			t_R = 4.45 $[M+H]^+$: 633.70
176			t_R = 4.99 $[M+H]^+$: 674.95

Table 33:



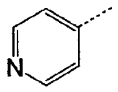
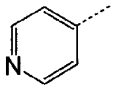
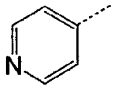
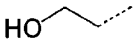
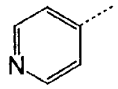
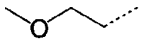
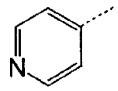
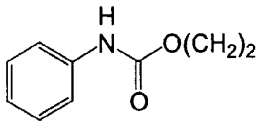
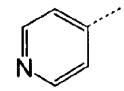
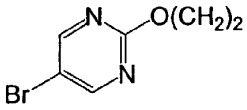
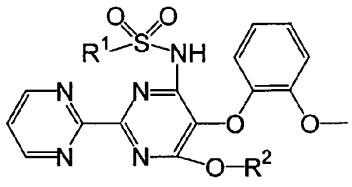
Ex. No.	R^1	R^2	LC-MS
177			t_R = 4.54 $[M+H]^+$: 508.22
178			t_R = 4.62 $[M+H]^+$: 532.23
179			t_R = 3.90 $[M+H]^+$: 538.33
180			t_R = 4.46 $[M+H]^+$: 552.27
181			t_R = 4.78 $[M+H]^+$: 657.46
182			t_R = 4.91 $[M+H]^+$: 696.51

Table 34:



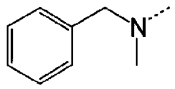
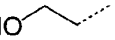
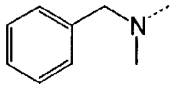
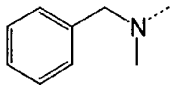
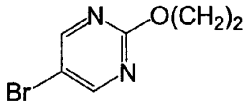
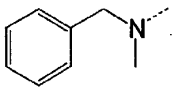
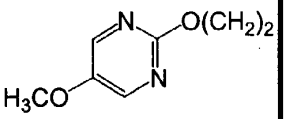
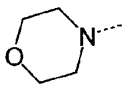
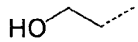
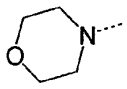
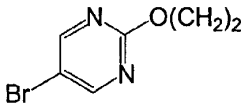
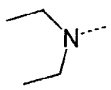
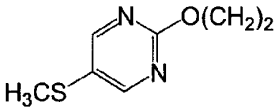
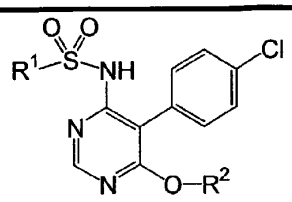
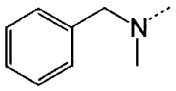
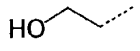
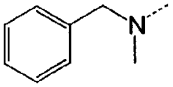
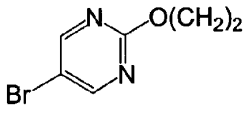
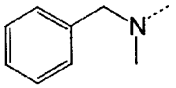
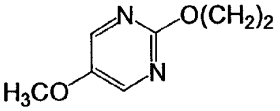
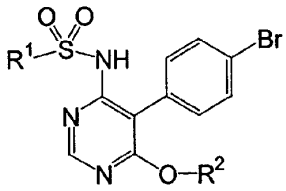
Ex. No.	R^1	R^2	LC-MS
185			t_R = 4.84 $[M-H]^+$: 507.15
186			t_R = 4.51 $[M+H]^+$: 539.47
187			t_R = 5.18 $[M-H]^+$: 695.09
188			t_R = 4.86 $[M+H]^+$: 647.43
189			t_R = 3.56 $[M+H]^+$: 505.35
190			t_R = 4.38 $[M+H]^+$: 663.05
191			t_R = 4.77 $[M+H]^+$: 615.32

Table 35:



Ex. No.	R^1	R^2	LC-MS
192			t_R = 4.84 $[M-H]^+$: 447.17
193			t_R = 5.66 $[M+H]^+$: 607.22
194			t_R = 5.31 $[M+H]^+$: 557.42



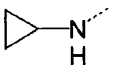
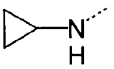
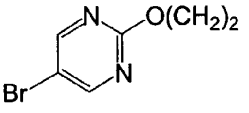
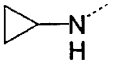
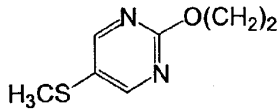
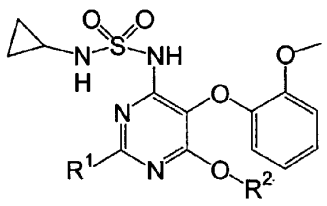
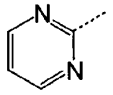
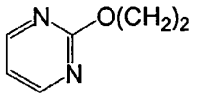
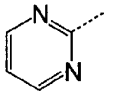
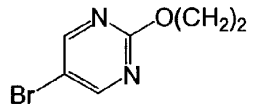
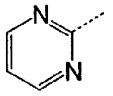
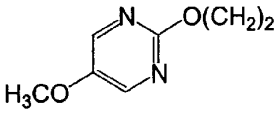
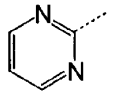
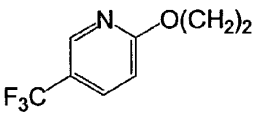
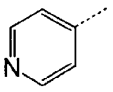
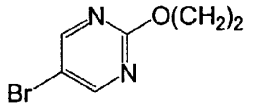
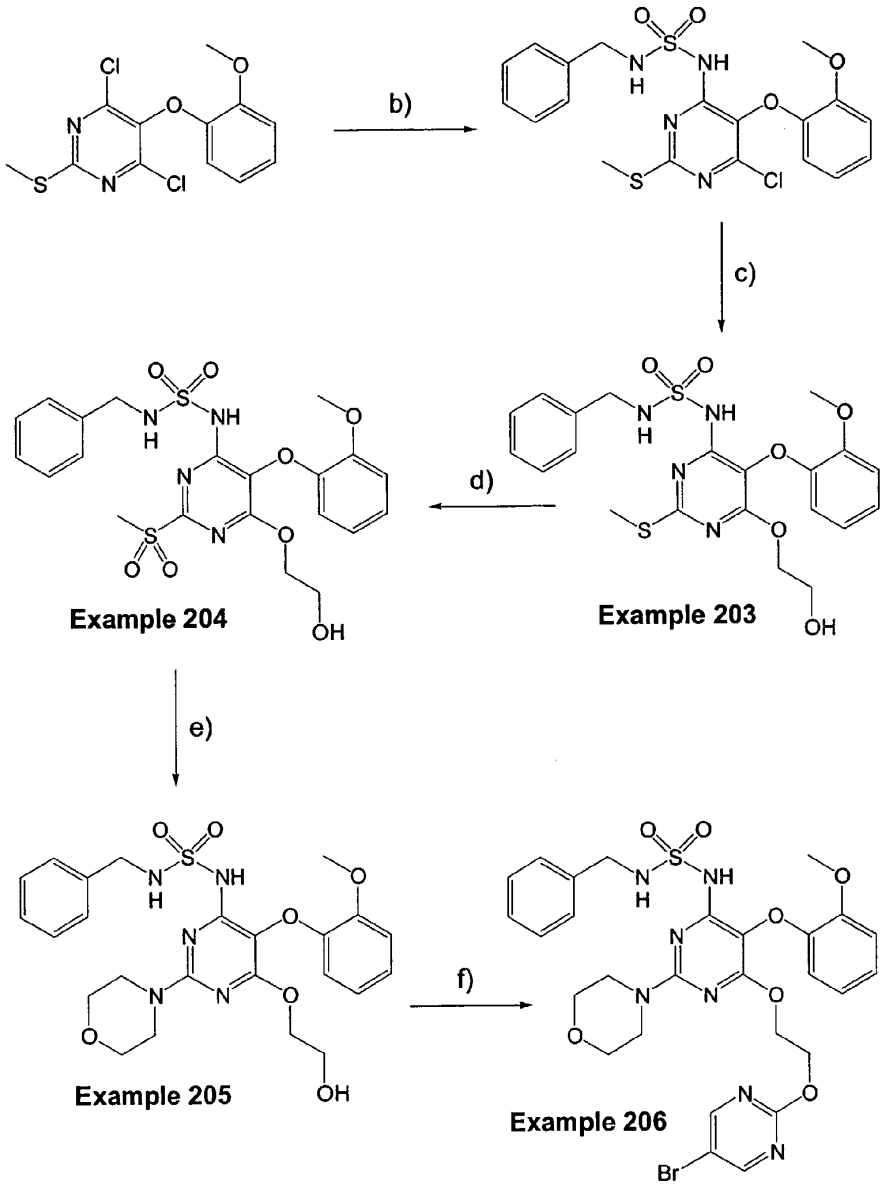
195			t_R = 3.92 $[M+H]^+$: 431.09
196			t_R = 4.99 $[M+H]^+$: 587.13
197			t_R = 4.90 $[M+H]^+$: 555.18

Table 36:



Ex. No.	R^1	R^2	LC-MS
198			t_R = 4.11 $[M+H]^+$: 551.34
199			t_R = 4.61 $[M+H]^+$: 633.37
200			t_R = 4.35 $[M+H]^+$: 583.40
201			t_R = 5.05 $[M+H]^+$: 617.98
202			t_R = 4.51 $[M+H]^+$: 632.16

Example 203 – 206:



a) According to the procedures described in [5], the preparation of 4,6-dichloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidine was achieved by the condensation of thiourea (6.4 g) with 2-(2-methoxy-phenoxy)-malonic acid dimethyl ester (20.32 g) followed by reacting the 2-mercapto-5-(2-methoxy-phenoxy)-pyrimidine-4,6-diol with methyliodide (5.9 ml) and subsequent chlorination with phosphorus oxychloride / N,N-dimethylaniline. Yield: 18.6 g; LC-MS: t_R = 5.73; $[M+H]^+$ = 318.2.

b) 4,6-Dichloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidine (1.5 g) was dissolved in DMSO (30 ml) and benzylsulfamic acid amide potassium salt (2.12 g, Referential Example 22) was added. Stirring was continued for 18 h. The reaction mixture was poured onto water, acidified by solid citric acid (1.9 g), cooled to 0°C and the precipitate was filtered off and purified by column chromatography over silica gel with hexane / EtOAc = 2 / 1 to give benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.75 g) as a white powder. LC-MS: t_R = 5.27; $[M+H]^+$ = 467.04.

c) Benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.75 g) was added to a solution of potassium tert.-butylate (1.87 g) in ethylene glycol (30 ml) and stirred at 100°C for 40 h. The reaction mixture was poured onto water (120 ml), acidified with solid citric acid (1.9 g) and cooled to 0°C. The precipitate was filtered off, washed with water and dried at HV to give benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (**Example 203**). LC-MS: t_R = 4.70; $[M+H]^+$ = 493.09.

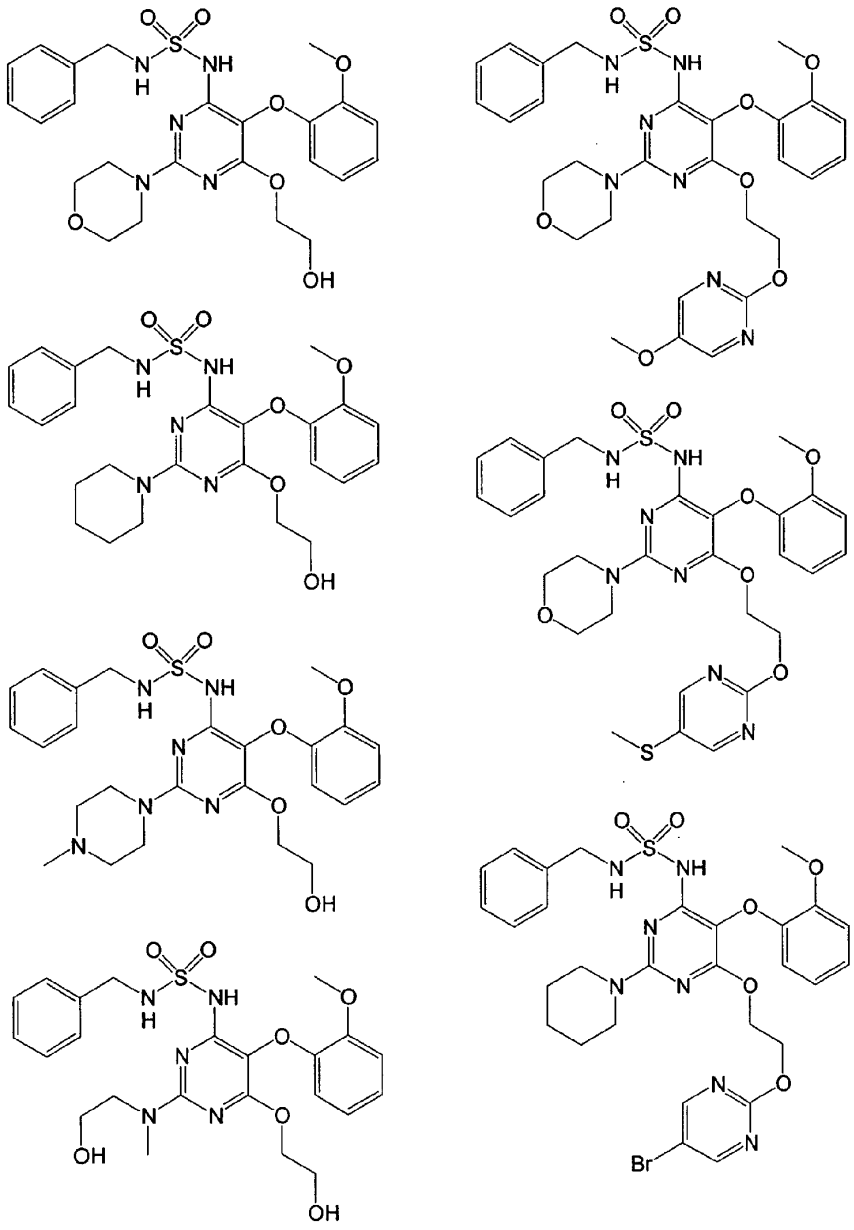
d) Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-methylsulfanyl-pyrimidin-4-yl]-amide (1.49 g) was dissolved in DCM (50 ml) and cooled to 0°C followed by slow addition of m-chloroperbenzoic acid (1.65 g; 70%) dissolved in DCM (15 ml). Stirring was continued for 30 min at 0°C and for 1.5 h at rt. The mixture was concentrated in vacuo until the product started to precipitate. The product was filtered off and purified by chromatography through

silicagel with EtOAc / hexane = 2 : 1 to give benzylsulfamic acid [6-(2-hydroxy-ethoxy)-2-methanesulfonyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (**Example 204**) (1.4 g) as a white powder. LC-MS: t_R = 4.12; $[M+H]^+$ = 525.09.

e) Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-2-methanesulfonyl-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (85 mg) were dissolved in THF (2 ml) and morpholine (2 ml) was added. The reaction mixture was stirred at 45°C for 48 hours, poured onto water, acidified with solid citric acid and extracted with EtOAc (2x). The combined EtOAc layers were washed with 10% citric acid solution and with brine, dried over magnesium sulfate, filtered and the solvent was evaporated. The crude product was purified by chromatography on plates with toluene / EtOAc = 1 / 1 to give benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (**Example 205**) (60 mg). LC-MS: t_R = 4.69; $[M+H]^+$ = 532.15.

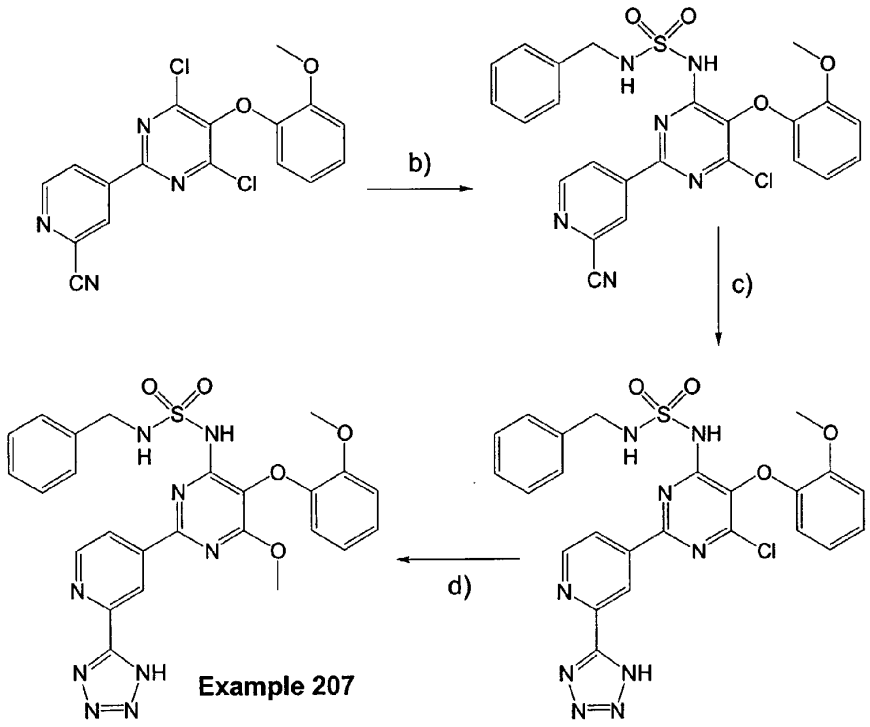
f) Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (**Example 206**) (40 mg) {LC-MS: t_R = 5.63; $[M+H]^+$ = 690.50} was prepared accoridng to the procedure described in Examples 5, 12 and 14 from benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-morpholin-4-yl-pyrimidin-4-yl]-amide (**Example 205**) (50 mg).

According to the procedures described for the preparation of Examples 203 – 206, the following compounds can be prepared:



The preparation of compounds by the above described procedures is not limited to the molecules schematically depicted. Further variations, especially also in the sulfamide part of the molecule, can be achieved via the same pathway.

Example 207:



Example 207

a) 4-[4,6-Dichloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carbonitrile can be prepared as described in WO 96/19459 and WO 00/42035.

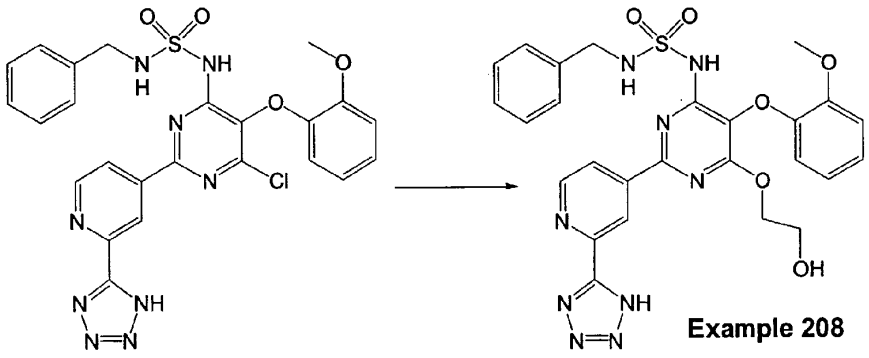
b) 4-[4,6-Dichloro-5-(2-methoxy-phenoxy)-pyrimidin-2-yl]-pyridine-2-carbonitrile (3.2 g) was dissolved in DMSO (20 ml), N-ethyldiisopropylamine (1.7 ml) and benzylsulfamic acid amide potassium salt (3.52 g) was added. The mixture was stirred for 18 h at rt, poured onto ice/water, acidified with solid citric acid and the precipitate was filtered off and recrystallized form EtOAc to give benzylsulfamic acid [6-chloro-2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (4.17 g). LC-MS: t_R = 5.55; $[M+H]^+$ = 523.29.

c) Benzylsulfamic acid [6-chloro-2-(2-cyano-pyridin-4-yl)-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide (4.17 g) was dissolved in DMF (55 ml). Sodium azide (5.2 g) and ammonium chloride (4.28 g) were added and the mixture was stirred for 20 h at 80°C. Then the mixture was pored onto water and extracted with EtOAc. The

layers were separated and the water layer was acidified with acetic acid to pH ~5 and extracted with EtOAc. The combined organic layers from the 2nd extraction were washed with brine, dried over magnesium sulfate, filtered and evaporated. The crude material was purified by chromatography over silicagel with EtOAc / MeOH / ammonia = 5 / 1 / 0.5 to give benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (1.67 g). LC-MS: t_R = 5.02; $[M+H]^+$ = 566.36.

d) According to the procedures described in Examples 1, 8 and 9, benzylsulfamic acid [6-chloro-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl}-amide (150 mg) was transformed to benzylsulfamic acid [6-methoxy-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (50 mg) (**Example 207**). LC-MS: t_R = 4.84; $[M+H]^+$ = 562.29.

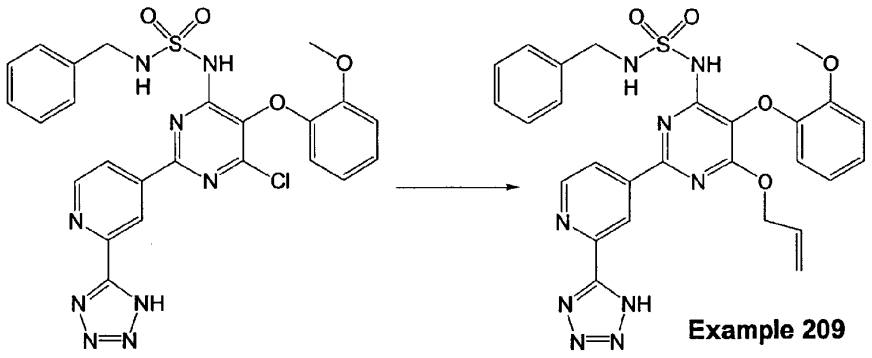
Example 208:



Example 208

Benzylsulfamic acid [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (1.5 g) was prepared according to the procedure described in Example 207d. LC-MS: t_R = 4.28; $[M+H]^+$ = 592.63.

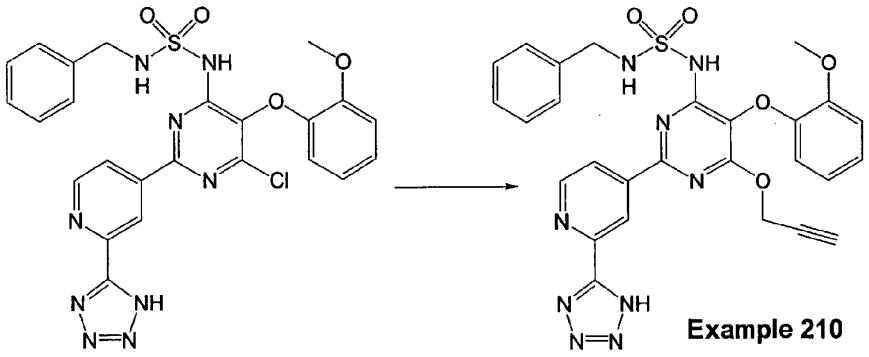
Example 209:



Example 209

Benzylsulfamic acid [6-allyloxy-5-(2-methoxy-phenoxy)-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (94 mg) was prepared according to the procedure described in Example 207d. LC-MS: t_R = 4.96; $[M+H]^+$ = 588.70.

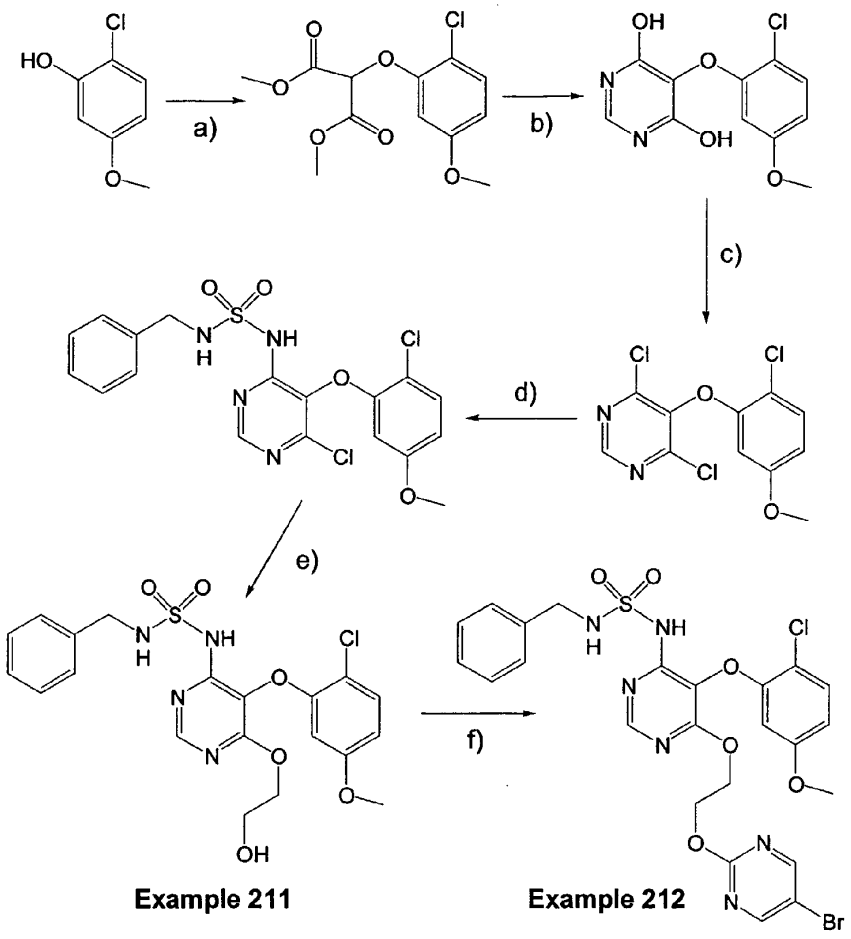
Example 210:



Example 210

Benzylsulfamic acid [5-(2-methoxy-phenoxy)-6-prop-2-ynyloxy-2-[2-(1H-tetrazol-5-yl)-pyridin-4-yl]-pyrimidin-4-yl]-amide (100 mg) was prepared according to the procedure described in Example 207d. LC-MS: t_R = 4.77; $[M+H]^+$ = 486.51.

Example 211 - 212:



Example 211 **Example 212**

2-Chloro-5-methoxy-phenol was prepared according to procedures described in the literature [M. Julia, J. de Rosnay; *Chimie Thérapeutique*, **1969**,*4*, p 334 – 343.]

a) 2-Chloro-5-methoxy-phenol was reacted with chloro dimethyl malonate in acetone and potassium carbonate according to the procedure described in Referential Example 1b to give 2-(2-chloro-5-methoxy-phenoxy)-malonic acid dimethyl ester.

b) 5-(2-Chloro-5-methoxy-phenoxy)-pyrimidine-4,6-diol was prepared from 2-(2-chloro-5-methoxy-phenoxy)-malonic acid dimethyl ester and formamidine hydrochloride according to the procedure described in Referential Example 1c.

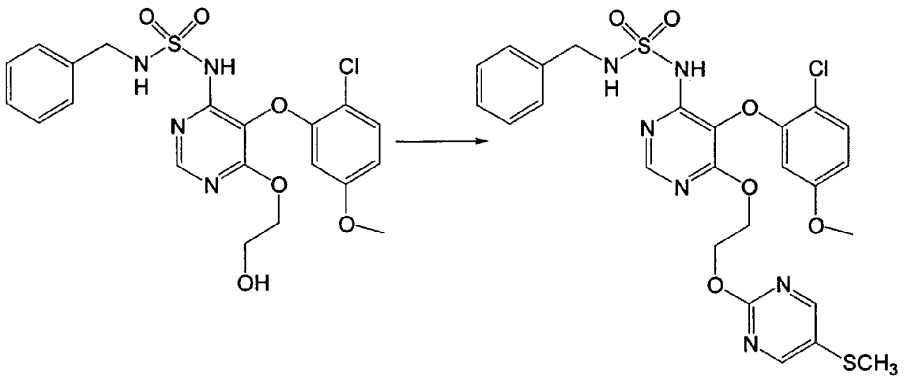
c) 4,6-Dichloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine was prepared from 5-(2-Chloro-5-methoxy-phenoxy)-pyrimidine-4,6-diol according to the procedure described in Referential Example 3b. LC-MS: t_R = 5.18; $[M+H]^+$ = 306.40; ^{1}H-NMR ($CDCl_3$): 8.7ppm (s, 1H); 7.4ppm (d, 1H); 6.6ppm (d, 1H); 6.02ppm (s, 1H); 3.86ppm (s, 3H).

d) Benzylsulfamic acid [6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (0.7 g) was prepared from 4,6-dichloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidine (1 g) and benzylsulfamic acid amide potassium salt (1.21 g) according to the procedure described in Referential Example 15. LC-MS: t_R = 5.13; $[M+H]^+$ = 456.91.

e) Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (0.6 g) (**Example 211**) was prepared from benzylsulfamic acid [6-chloro-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (0.697 g) according to the procedure described in Example 3,10 or 13. LC-MS: t_R = 4.50; $[M+H]^+$ = 481.12.

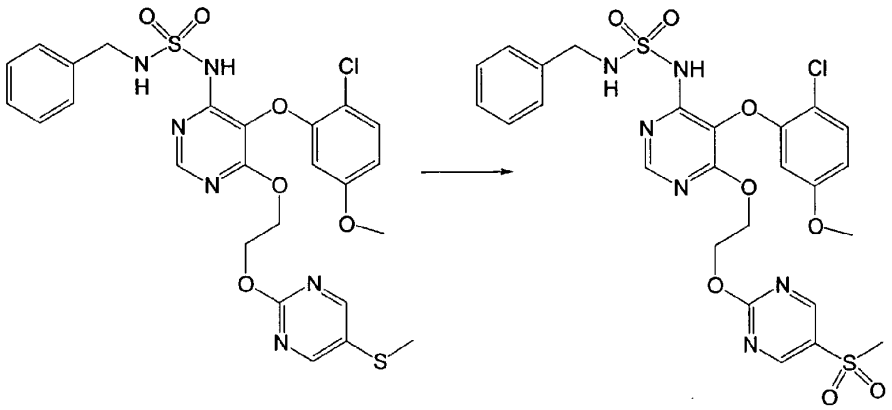
f) Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (77 mg) (**Example 212**) was prepared from benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (120 mg) (**Example 211**) and 5-bromo-2-chloropyrimidine (100 mg) according to the procedure described in Example 14. LC-MS: t_R = 5.29; $[M+H]^+$ = 639.04.

Example 213:



Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (138 mg) (**Example 213**) was prepared from benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-(2-hydroxy-ethoxy)-pyrimidin-4-yl]-amide (240 mg) (**Example 211**) and 5-methylsulfanyl-2-chloropyrimidine (180 mg) according to the procedure described in Example 14. LC-MS: t_R = 5.22; $[M+H]^+$ = 606.75.

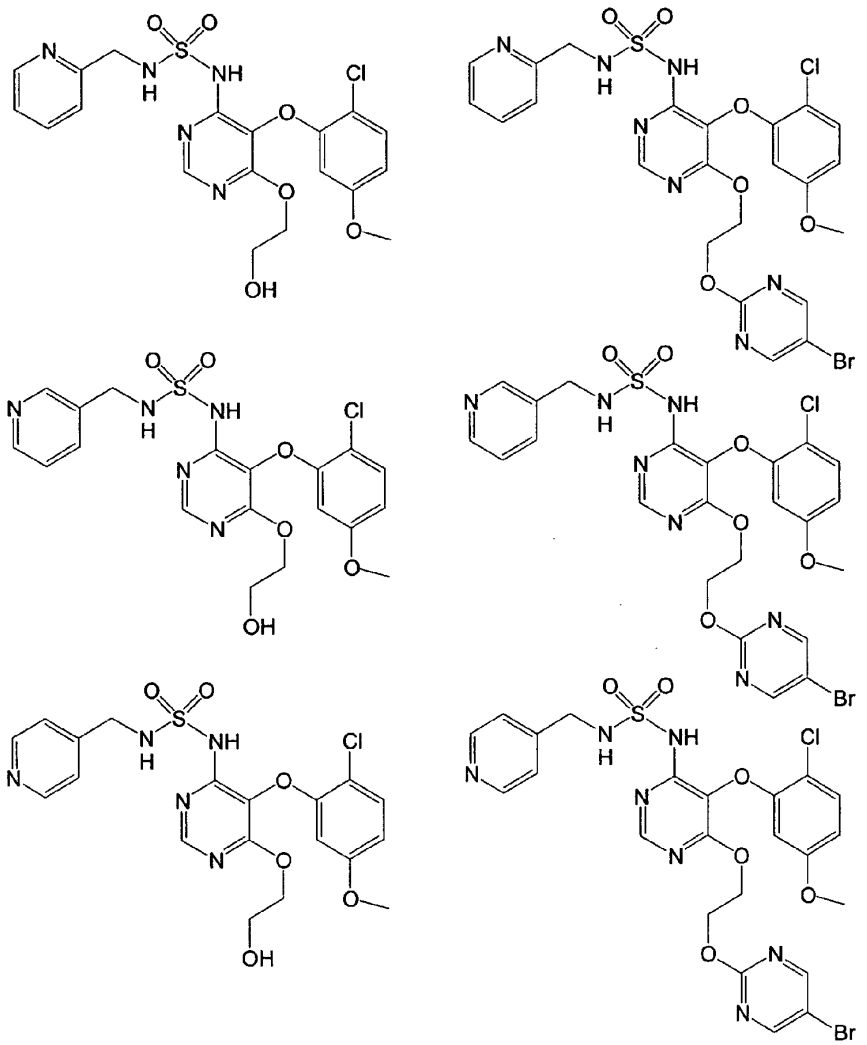
Example 214:



Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methanesulfonyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide (47 mg) (**Example 214**) was prepared by oxidation of benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(2-chloro-5-methoxy-phenoxy)-pyrimidin-4-yl]-amide (80 mg)

(**Example 213**) with peracetic acid according to general procedures described in the literature. LC-MS: t_R = 4.72; $[M-H]^+$ = 635.05.

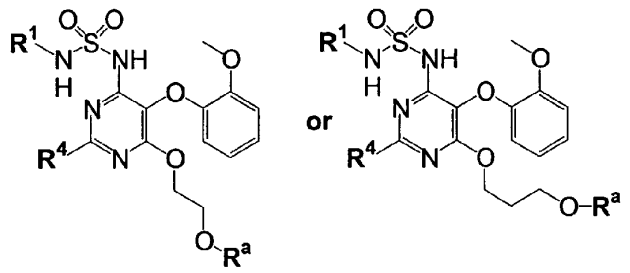
According to the procedures described for the preparation of Examples 211 – 214, the following compounds can be prepared:



The preparation of compounds by the above described procedures is not limited to the molecules schematically depicted. Further variations, especially in the sulfamide-part and at the side chain in position 6 of the core pyrimidine ring of the molecule, can be achieved via the same pathway.

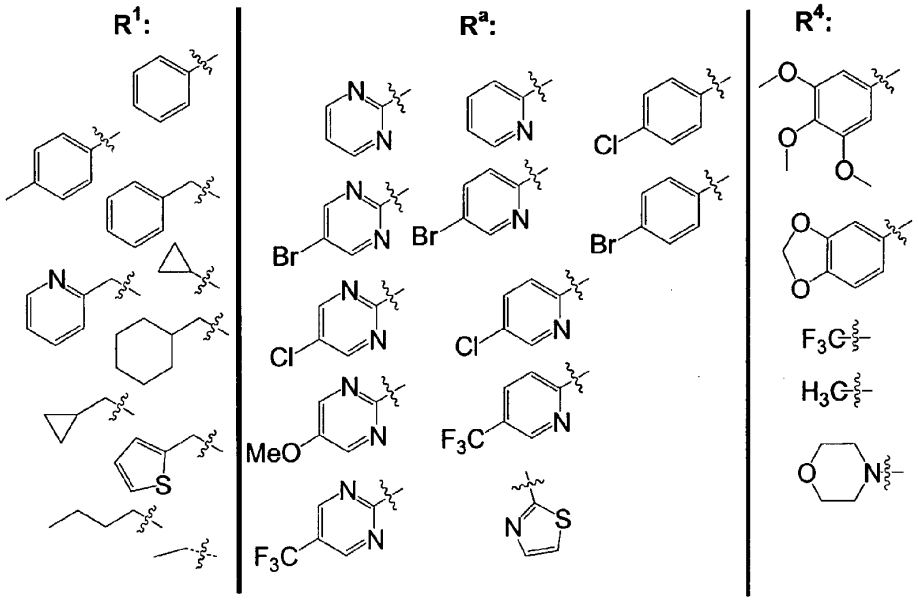
Example 215:

Using methods described in the above Examples and in Schemes 1 to 4 and the cited references, the compounds disclosed in Table a) can be prepared:



or

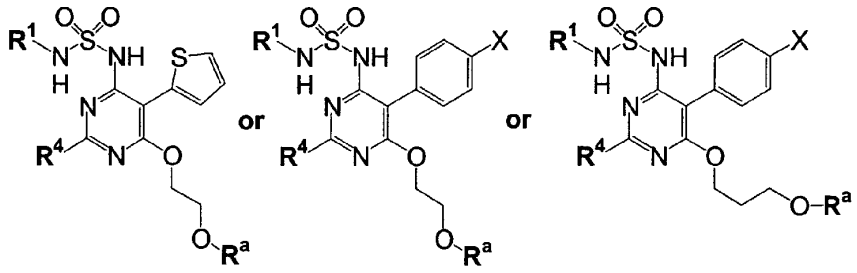
Table a:



indicates the connection of the substituents to the respective atom of the core unit

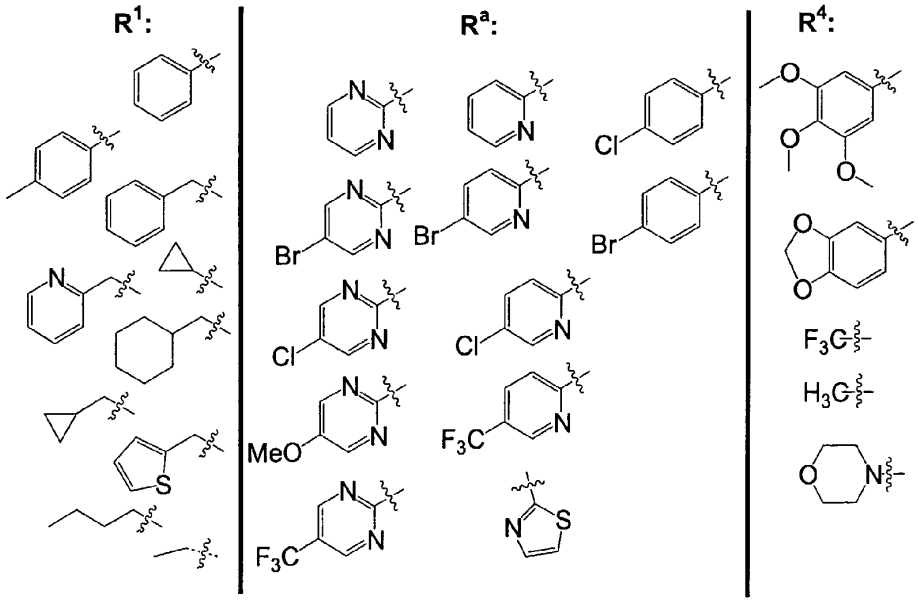
Example 216:

Using methods described in the above Examples and in Schemes 1 to 4 and in the cited references, the compounds disclosed in Table b) can be prepared:



X = H; CH_3; Cl; Br; OCH_3; F; CF_3; CH_2CH_3

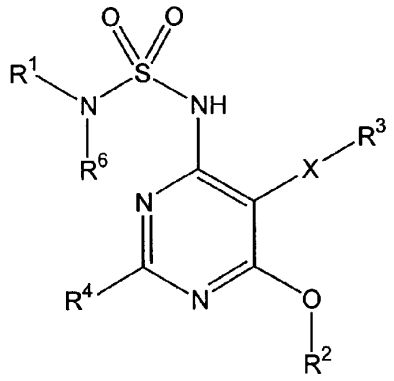
Table b:



-§- indicates the connection of the substituents to the respective atom of the core unit

Claims

1. Compounds of the general formula I



General Formula I

wherein

R^1 represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; cycloalkyl; cycloalkyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; lower alkyl; hydrogen; or may form a heterocyclyl- or cycloalkyl-ring together with R^6;

R^2 represents $-CH_3$; $-(CH_2)_n-Y-R^a$; $-(CH_2)_m-C\equiv C-(CH_2)_p-Z-R^a$; $-(CH_2)_k-C(R^b)=CR^cR^d$; $-CH_2$-tetrahydrofuran-2-yl;

R^3 represents aryl; heteroaryl;

R^4 represents hydrogen; trifluoromethyl; lower alkyl; lower alkyl-amino; lower alkyloxy; lower alkyloxy-lower alkyloxy; hydroxy-lower alkoxy; lower alkyl-sulfinyl; lower alkylthio; lower alkylthio-lower alkyl; hydroxy-lower alkyl; lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-oxy-lower alkyl; hydroxy-lower alkyl-amino; lower alkyl-amino-lower alkyl; amino; di-lower alkyl-amino; [N-(hydroxy-lower alkyl)-N-(lower alkyl)]-amino; aryl; aryl-amino; aryl-lower alkyl-amino; aryl-thio; aryl-lower alkyl-thio; aryloxy; aryl-lower alkyl-oxy; aryl-lower alkyl; aryl-sulfinyl; heteroaryl; heteroaryl-oxy; heteroaryl-lower alkyl-oxy; heteroaryl-amino; heteroaryl-lower alkyl-amino; heteroaryl-thio; heteroaryl-lower alkyl-thio; heteroaryl-lower alkyl; heteroaryl-sulfinyl; heterocyclyl; heterocyclyl-lower alkyl-oxy; heterocyclyl-oxy;

heterocyclyl-amino; heterocyclyl-lower alkyl-amino; heterocyclyl-thio; heterocyclyl-lower alkyl-thio; heterocyclyl-lower alkyl; heterocyclyl-sulfinyl; cycloalkyl; cycloalkyl-oxy; cycloalkyl-lower alkyl-oxy; cycloalkyl-amino; cycloalkyl-lower alkyl-amino; cycloalkyl-thio; cycloalkyl-lower alkyl-thio; cycloalkyl-lower alkyl; cycloalkyl-sulfinyl;

R^6 represents hydrogen; lower alkyl; or may form a heterocyclyl- or cycloalkyl-ring together with R^1;

X represents oxygen; sulfur; $-CH_2-$ or a bond;

Y represents a bond, -O-; -NH-; $-NH-SO_2-$; $-NH-SO_2-NH-$; O-CO-; -CO-O-; -O-CO-NH-; -NH-CO-O-; -NH-CO-NH-

Z represents oxygen or a bond;

k represents the whole numbers 1, 2, 3, 4, 5 or 6;

n represents the whole numbers 2, 3, 4, 5 or 6;

m represents the whole numbers 1, 2, 3, 4 or 5;

p represents the whole numbers 0 (zero), 1, 2 or 3 and if p represents the whole number 0 (zero), Z cannot represent oxygen;

R^a represents aryl; heteroaryl; lower alkyl; cycloalkyl; hydrogen;

R^b and R^c independently represent hydrogen or lower alkyl;

R^d represents represents hydrogen; lower alkyl; aryl; heteroaryl;

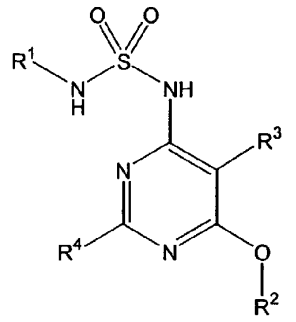
and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

2. Compounds of the formula I in claim 1, wherein R^1, R^2 and R^4 are as defined in general formula I in claim 1, **X** represents oxygen and R^3 represents phenyl or mono-substituted phenyl substituted with halogen, lower alkyl, lower alkoxy and lower alkanoyl;
and pharmaceutically acceptable salts of compounds of general formula I.

3. Compounds of the formula I in claim 1, wherein R^1 and R^4 are as defined in general formula I in claim 1, **X** represents oxygen, R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy and R^2 represents $-(CH_2)_n$-Y-R^a, wherein **n**, **Y** and R^a are as defined in general formula I in claim 1;
and pharmaceutically acceptable salts of compounds of general formula I.

4. Compounds of the formula I in claim 1, wherein R^1 and R^4 are as defined in general formula I in claim 1, **X** represents oxygen, R^3 represents phenyl or mono-substituted phenyl substituted with lower alkoxy and R^2 represents $-(CH_2)_2$-O-R^a, wherein R^a is as defined in general formula I in claim 1;
and pharmaceutically acceptable salts of compounds of general formula I.

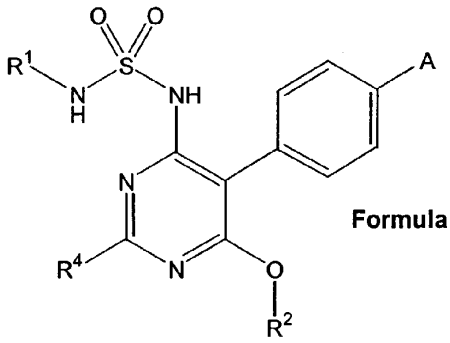
5. Compounds of formula II



Formula II

wherein R^1, R^2, R^3 and R^4 are as defined in general formula I in claim 1 above and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula II.

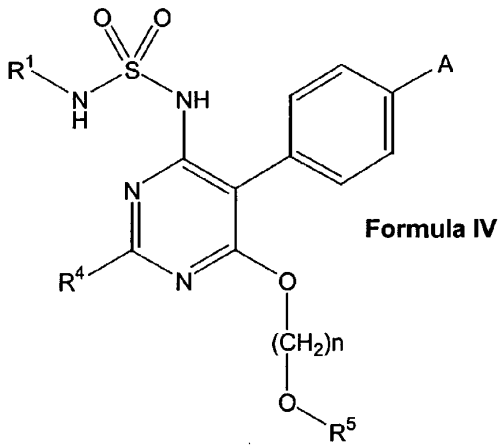
6. Compounds of formula III



Formula III

wherein R^1, R^2 and R^4 are as defined in general formula I in claim 1 above and **A** represents hydrogen, methyl, ethyl, chlorine, bromine, fluorine, trifluoromethyl or methoxy and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula III.

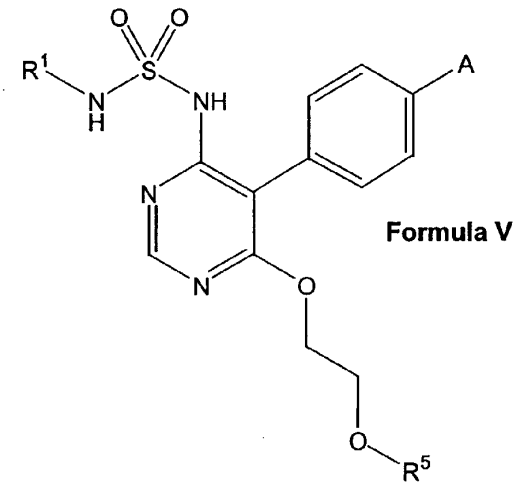
7. Compounds of the formula IV



Formula IV

wherein R^1, R^4 and **n** are as defined in general formula I in claim 1 above and **A** is as defined in formula III in claim 6 above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

8. Compounds of formula V



Formula V

wherein R^1 is as defined in general formula I in claim 1 above, **A** is as defined in formula III in claim 6 above and R^5 represents hydrogen, lower alkyl, aryl, heteroaryl and cycloalkyl, and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts of compounds of formula IV.

9. Compounds according to claim 8, wherein R^5 in formula V in claim 8 represents heteroaryl and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof.

10. The compounds selected from claims 1 to 9

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Pyridin-2-yl-carbamic acid 2-[5-(2-methoxy-phenoxy)-6-(4-methoxy-benzylsulfamic acid amido)-[2,2']bipyrimidinyl-4-yloxy]-ethyl ester;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Cyclopropylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-[2,2']bipyrimidinyl-4-yl]-amide;

Benzylsulfamic acid-[6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(2-methoxy-phenoxy)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid-[5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-2-pyridin-4-yl-5-p-tolyl-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-2-pyridin-4-yl-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-(4-chloro-phenyl)-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [5-(2-chloro-5-methoxy-phenoxy)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Benzylsulfamic acid [6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-5-(4-bromo-phenyl)-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

and pharmaceutically acceptable salts thereof.

11. The compounds selected from claims 1 to 9

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-3-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Pyridin-4-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

4-Fluorobenzylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Furan-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Thiophen-2-yl-methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Methylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Ethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Propylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Butylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopentylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

Cyclopropylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-bromo-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methoxy-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

N-Benzylmethylsulfamic acid [5-(4-chloro-phenyl)-6-[2-(5-methylsulfanyl-pyrimidin-2-yloxy)-ethoxy]-pyrimidin-4-yl]-amide;

and pharmaceutically acceptable salts thereof.

12. Pharmaceutical compositions for the treatment of disorders which are associated with a role of endothelin, especially circulatory disorders such as hypertension, ischaemia, vasospasm and angina pectoris and proliferative disorders such as cancer, containing a compound of any one of claims 1 to 11 and usual carrier materials and adjuvants.

13. Pharmaceutical compositions for the treatment of disorders which are associated with a role of endothelin, such as migraine, asthma, hyperlipidemia or inflammatory disorders, containing a compound of any one of claims 1 to 11 and usual carrier materials and adjuvants.

14. The compounds of any one of the claims 1 to 11 for use as medicaments for the treatment of disorders which are associated with a role of endothelin, especially circulatory disorders such as hypertension, ischaemia, vasospasm and angina pectoris, hyperlipidemia, proliferative disorders such as cancer, migraine and inflammatory disorders.

15. The compounds of any one of the claims 1 to 11 for use as medicaments for the treatment of disorders which are associated with a role of endothelin, and require blocking both ET_A and ET_B receptors.

16. The compounds of any one of the claims 1 to 11 for use as medicaments for the treatment of disorders which are associated with a role of endothelin, and require selective ET_A–receptor blocking for treatment.

17. The compounds of any one of the claims 1 to 11 for use as medicaments for the treatment of disorders which are associated with a role of endothelin, and require selective ET_B–receptor blocking for treatement.

18. The use of one or more compounds of any one of claims 1 to 11 as active ingredients for the production of pharmaceutical compositions for the treatment of disorders associated with a role of endothelin, especially circulatory disorders such as hypertension, ischaemia, vasospasm and angina pectoris and proliferative disorders such as cancer.

19. The use of one or more compounds of any one of claims 1 to 11 as active ingredients for the production of pharmaceutical compositions for the treatement of disorders associated with endothelin activities, such as migraine, asthma, hyperlipidemia or inflammatory disorders.

20. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with a role of endothelin containing one or more compounds as claimed in any one of claims 1 to 11 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.

21. The novel compounds, processes and methods as well as the use of such compounds substantially as described herein before.

EXHIBIT C

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(54) Title: ENDOTHELIN A RECEPTOR (ET_A) ANTAGONISTS IN COMBINATION WITH PHOSPHODIESTERASE 5 INHIBITORS (PDE5) AND USES THEREOF

(57) Abstract: The invention relates generally to combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor, pharmaceutical compositions comprising ET_A antagonist and PDE5 inhibitor and methods of treating various disorders comprising administering an ET_A antagonist and a PDE5 inhibitor. In particular, the combination therapies and pharmaceutical compositions are useful for the treatment and/or prevention of cardiac disorders such as pulmonary arterial hypertension (PAH).

ENDOTHELIN A RECEPTOR (ET_A) ANTAGONISTS IN COMBINATION WITH PHOSPHODIESTERASE 5 INHIBITORS (PDE5) AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims the benefit of U.S. Provisional Application No. 60/604,462, filed August 26, 2004, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[002] The invention relates generally to combination therapies comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor, pharmaceutical compositions comprising ET_A antagonist and PDE5 inhibitor and methods of treating various disorders comprising administering an ET_A antagonist and a PDE5 inhibitor . In particular, the combination therapies and pharmaceutical compositions are useful for the treatment and/or prevention of cardiac disorders such as pulmonary arterial hypertension (PAH).

BACKGROUND OF THE INVENTION

[003] Systemic hypertension, also called high blood pressure, is a condition in which the blood pressure in either arteries or veins is abnormally high. Blood pressure is defined as the force exerted by the blood against the walls of the blood vessels. Normally, the pumping of the heart creates a rhythmic pulsing of blood along and against the walls of the blood vessels, which are flexible enough to dilate or contract and thus keep the pressure constant. Most physicians consider the normal systemic blood pressure of a healthy adult to be approximately 120/80--i.e., equivalent to the pressure exerted by a column of mercury 120 mm high during contraction of the heart (systole) and 80 mm high during relaxation (diastole). However, for a variety of reasons, the blood vessels may lose their flexibility, or the muscles surrounding them may force them to contract. As a result, the heart must pump more forcefully to move the same amount of blood through the narrowed vessels into the capillaries, thereby increasing the blood pressure. Regardless of the mechanism, a sustained elevation of blood pressure for a period of time has been shown to result in significant cardiovascular damage throughout the body, *e.g.*, congestive heart failure, coronary artery disease, stroke and progressive renal failure. Congestive heart failure frequently

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constitutes an end-stage complication of cardiac overload due to systemic hypertension or cardiac valve dysfunctions but may also result from acute or chronic ischemic heart disease and idiopathic cardiomyopathies (Battegay, J. Mol. Med., 73:333 (1995)). Patients suffering from systemic hypertension or aortic valve dysfunction can benefit from adequate drug treatment or valve replacements, but hypertrophy and heart failure may become irreversible (Golia et al., Int. J. Cardiol., 60:81 (1997)).

[004] Systemic hypertension is generally classified by cause, either as essential (of unknown origin) or as secondary (the result of a specific disease, disorder or other condition). Secondary hypertension may result from a wide range of causes. For example, renal hypertension affects the entire systemic circulation and arises from hypertension within the renal arteries, which branch from the aorta to supply blood to the kidneys. Hypertension may also result from the excess hormones that are secreted during abnormal functioning of the outer substance, or cortex, of the adrenal glands (Cushing's syndrome; aldosteronism); from the excess hormones resulting from pheochromocytoma, which is a tumor of the inner substance (medulla) of the adrenal glands; or from the excess hormones secreted by pituitary tumors. Other causes of secondary hypertension are coarctation--localized narrowing--of the aorta, pregnancy, and the use of oral contraceptives. In all secondary cases, the hypertension is relieved by treating the underlying condition or cause. By far the most common form of hypertension (90 percent of cases) is essential, or idiopathic, hypertension. Although no specific cause can be determined in such cases, studies have pointed out several contributing factors. Included among these are a family history of hypertension, obesity, high salt intake, smoking, and most importantly, emotional and physical stress.

[005] In its milder forms, essential hypertension is usually treated with a self-help regimen that includes a no-salt diet and perhaps a weight-reducing diet, a decrease in or cessation of smoking, mild exercise, and the avoidance of or successfully coping with stressful situations. If a self-help program does not help lower the patient's blood pressure, the physician will usually prescribe diuretics or sympathetic-nerve blockers. The nerve blockers generally act by decreasing heart output and peripheral resistance to blood flow. Beta blockers are the most commonly used of these drugs and include metoprolol, nadolol, and propranolol. More severe hypertension often requires the use of drugs called vasodilators, which dilate the arteries, thus lowering blood pressure.

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Oral vasodilators, which include hydralazine and minoxidil, are often used in conjunction with a diuretic and a sympathetic nerve blocker to inhibit the body's natural tendency to increase fluid retention and increase blood flow in response to the arterial dilation. Severe and immediately life-threatening hypertension, either secondary or essential, is called malignant hypertension and usually requires hospitalization and acute medical care. Treatment includes the intravenous administration of vasodilators such as diazoxide.

[006] Cyclic nucleotide second messengers (cAMP and cGMP) play a central role in signal transductions and regulation of physiologic responses, such as vasodilation. Their intracellular levels are controlled by the complex superfamily of cyclic nucleotide phosphodiesterase (PDE) enzymes. Inhibitors of PDE are agents that can either activate or suppress PDEs via allosteric interaction with the enzymes or binding to the active site of the enzymes. The PDE family includes at least 19 different genes and at least 11 PDE isozyme families, with over 50 isozymes having been identified thus far. The PDEs are distinguished by (a) substrate specificity, i.e., cGMP-specific, cAMP-specific or nonspecific PDEs, (b) tissue, cellular or even sub-cellular distribution, and (c) regulation by distinct allosteric activators or inhibitors. PDE inhibitors include both nonspecific PDE inhibitors and specific PDE inhibitors (those that inhibit a single type of phosphodiesterase with little, if any, effect on any other type of phosphodiesterase).

[007] Pulmonary arterial hypertension (PAH) is a condition that involves high blood pressure and structural changes in the walls of the pulmonary arteries, which are the blood vessels that connect the right side of the heart to the lungs. PAH causes shortness of breath, limits activity, and is eventually fatal unless treated successfully with heart and lung transplant. Primary and secondary PAH are estimated to afflict approximately 80,000 to 100,000 people worldwide, many of whom are children and young women.

[008] Standard management of patients with PAH includes anticoagulant therapy with warfarin (COUMADIN, and others) in combination with a diuretic such as furosemide (LASIX, and others) to manage fluid retention caused by right-sided heart failure, and for selected patients, a calcium-channel blocker such as amlodipine (NORVASC) (JR Runo and JE Loyd, Lancet, 361:1533 (2003); JP Maloney, Curr. Opin. Pulm. Med., ;9:139 (2003)). One phosphodiesterase type 5 (PDE5) inhibitor, sildenafil

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(REVATIO), has recently been approved for treating PAH in 20 mg doses (TID). PDE5 is the main phosphodiesterase in the pulmonary vasculature; inhibiting it maintains high levels of cGMP, which promotes the vasodilating effects of endogenous nitric oxide (M Humbert and G Simonneau, Am. J. Respir. Crit. Care Med., 169:6 (2004)).

[009] However, PDE5s, such as sildenafil have several adverse effects. For instance, in intermittent use of sildenafil (VIAGRA) for erectile dysfunction, once-daily doses of 25-100 mg has caused headaches, dyspepsia and visual disturbances. Its most serious effect has been severe, sometimes fatal, hypotension in patients taking nitrates for angina pectoris (*see*, Abramowicz, ed., Sildenafil for Pulmonary Hypertension, The Medical Letter on Drugs and Therapeutics, Vol. 46, Issue 1177, (March 1, 2004) Therefore, it would be beneficial to provide a complimentary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors.

[010] Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms: ET-1, ET-2 and ET-3. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. The vasoconstricting effect is caused by the binding of endothelin to its receptor on the vascular smooth muscle cells (Nature, 332:411-415 (1988); FEBS Letters, 231:440-444 (1988); Biochem. Biophys. Res. Commun. 154:868-875 (1988)).

[011] Increased or abnormal release of endothelin causes persistent vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the literature that elevated levels of endothelin were found in the plasma of patients with hypertension, acute myocardial infarction, pulmonary hypertension, Raynaud's syndrome and atherosclerosis and in the airways of asthmatics (Japan J. Hypertension, 12:79 (1989); J. Vascular Med. Biology 2:207 (1990); J. Am. Med. Association 264:2868 (1990)).

[012] Two distinct endothelin receptors, designated ET_A and ET_B, have been identified, and DNA clones encoding each receptor have been isolated (Arai et al., Nature, 348(6303):730-732 (1990); Sakurai et al., Nature, 348(6303):732-735 (1990)). Based on the amino acid sequences of the proteins encoded by the cloned DNA, it appears that each receptor contains seven membrane-spanning domains and exhibits structural similarity to G-protein-coupled membrane proteins. Messenger RNA

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encoding both receptors has been detected in a variety of tissues, including heart, lung, kidney and brain. The distribution of receptor subtypes is tissue specific (Martin et al., Biochem. Biophys. Res. Commun., 162:130-137 (1989)). ET_A appears to be selective for endothelin-1 and is predominant in cardiovascular tissues. ET_B is predominant in noncardiovascular tissues, such as the central nervous system and kidney, and interact with the three endothelin isopeptides (Sakurai et al., Nature, 348(6303):732-735(1990)). In addition, ET_A occurs on vascular smooth muscle, is linked to vasoconstriction and has been associated with cardiovascular, renal and central nervous system diseases whereas ET_B is located on the vascular endothelium, is linked to vasodilation (Takayanagi et al., FEBS Letters., 282:103-106 (1991)) and has been associated with bronchoconstrictive disorders.

[013] By virtue of the distribution of receptor types and the differential affinity of each isopeptide for each receptor type, the activity of the endothelin isopeptides varies in different tissues. For example, endothelin-1 inhibits ^{125}I-labeled endothelin-1 binding in cardiovascular tissues forty to seven hundred times more potently than endothelin-3. ^{125}I-labeled endothelin-1 binding in non-cardiovascular tissues, such as kidney, adrenal gland, and cerebellum, is inhibited to the same extent by endothelin-1 and endothelin-3, which indicates that ET_A predominates in cardiovascular tissues and ET_B predominates in non-cardiovascular tissues.

[014] Endothelin plasma levels are elevated in certain disease states (*see, e.g.*, International Application No. WO 94/27979 and U.S. Pat. No. 5,382,569). Endothelin-1 plasma levels in healthy individuals, as measured by radioimmunoassay (RIA), are about 0.26-5 pg/ml. Blood levels of endothelin-1 and its precursor, big endothelin, are elevated in shock, myocardial infarction, vasospastic angina, kidney failure and a variety of connective tissue disorders. In patients undergoing hemodialysis or kidney transplantation or suffering from cardiogenic shock, myocardial infarction or pulmonary hypertension, blood levels of endothelin-1 as high as 35 pg/ml have been observed (*see*, Stewart et al., Annals Internal Med., 114:464-469 (1991)). Because endothelin is likely to be a local, rather than a systemic, regulating factor, it is probable that the levels of endothelin at the endothelium/smooth muscle interface are much higher than circulating levels.

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[015] Elevated levels of endothelin have also been measured in patients suffering from ischemic heart disease (Yasuda et al., Amer. Heart J., 119:801-806 (1990); Ray et al., Br. Heart J,. 67:383-386 (1992)). Circulating and tissue endothelin immunoreactivity is increased more than two-fold in patients with advanced atherosclerosis (Lerman et al., New Engl. J. Med., 325:997-1001 (1991)). Increased endothelin immunoreactivity has also been associated with Buerger's disease (Kanno et al., J. Amer. Med. Assoc., 264:2868 (1990)) and Raynaud's phenomenon (Zamora et al., Lancet, 336:1144-1147 (1990)). Increased circulating endothelin levels were observed in patients who underwent percutaneous transluminal coronary angioplasty (PTCA) (Tahara et al., Metab. Clin. Exp., 40:1235-1237 (1991); Sanjay et al., Circulation, 84(Suppl. 4):726 (1991)) and in individuals with pulmonary hypertension (Miyauchi et al., Jpn. J. Pharmacol., 58:279P (1992); Stewart et al., Ann. Internal Medicine, 114:464-469(1991)).

[016] A recent study in patients with congestive heart failure demonstrated a good correlation between the elevated levels of endothelin in the plasma and the severity of the disease.

[017] Endothelin is an endogenous substance that directly or indirectly (through the controlled release of various other endogenous substances) induces sustained contraction of vascular or non-vascular smooth muscles. Its excess production or excess secretion is believed to be one of the factors responsible for hypertension, pulmonary hypertension, Raynaud's disease, bronchial asthma, acute renal failure, myocardial infarction, angina pectoris, arteriosclerosis, cerebral vasospasm and cerebral infarction (*see* A. M. Doherty, Endothelin: A New Challenge., J. Med. Chem., 35:1493-1508 (1992)).

[018] Substances that specifically inhibit the binding of endothelin to its receptor are believed to block the physiological effects of endothelin and are useful in treating patients with endothelin-related disorders.

SUMMARY OF THE DISCLOSURE

[019] One embodiment of the invention is directed to a combination therapy comprising at least one endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor.

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[020] Another embodiment of the invention is directed to a combination therapy, wherein the ET_A antagonist and the PDE5 inhibitor are administered together or separately

[021] Another embodiment of the invention provides for the combination therapy to be a pharmaceutical composition, wherein the pharmaceutical composition is in an immediate release formulation or a controlled release formulation, wherein the ET_A antagonist is in a controlled release formulation, the PDE5 inhibitor is in a controlled release formulation or both are in a controlled release formulation. If both are in a controlled release formulation, the ET_A antagonist and the PDE5 inhibitor may be released at different rates.

[022] Another embodiment of the invention is directed to a pharmaceutical composition comprising endothelin A receptor (ET_A) antagonist, a phosphodiesterase 5 (PDE5) inhibitor and a pharmaceutical carrier.

[023] Another embodiment of the invention provides for the pharmaceutical composition to be in an immediate release formulation or a controlled release formulation, wherein the ET_A antagonist is in a controlled release formulation, the PDE5 inhibitor is in a controlled release formulation or both are in a controlled release formulation. If both are in a controlled release formulation, the ET_A antagonist and the PDE5 inhibitor may be released at different rates.

[024] Yet another embodiment provides for a method of reducing the side effects or toxicity of an ET_A antagonist, a PDE5 inhibitor or both comprising administering an ET_A antagonist and a PDE5 inhibitor, wherein the amount of the PDE5 required to treat a condition is reduced or modulated.

[025] Another embodiment of the invention is directed to a method of treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of a) a PDE5 inhibitor and b) an ET_A antagonist, wherein administration of a) and b) is concurrent or sequentially in either order.

[026] Another embodiment of the invention is directed to a method of effecting or facilitating the treatment of a vascular condition in a mammal comprising administering a therapeutically effective amount of an ET_A antagonist and a PDE5 inhibitor.

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[027] Another embodiment of the invention is directed to a method of treating pulmonary arterial hypertension comprising administering to a subject in need thereof a therapeutically effective amount of an ET_A antagonist and a PDE5 inhibitor.

[028] Another embodiment of the invention is directed to a method for treating a vascular condition comprising administering to a subject in need thereof a therapeutically effective amount of a combination of ET_A antagonist and a PDE5 inhibitor.

[029] For each of the recited embodiments described in the application, the ET_A antagonist may be selected from any one of the compounds described herein selective for the endothelin A receptor or as can be determined according to references cited herein, and the PDE_5 inhibitor may be selected from any one of the compounds described herein as selective for PDE5 or as can be determined according to references cited herein. One example for each of the recited embodiments comprises sitaxsentan as the ET_A antagonist and sildenafil, tadalafil (CIALIS), vardenafil (LEVITRA) or dasantafil as the PDE5 inhibitor. In another example for each of the recited embodiments described in the application, the combination comprises sitaxsentan and sildenafil. In yet another example for each of the recited embodiments described in the application, the combination comprises sitaxsentan and tadalafil.

[030] Embodiments of the invention are useful in treating vascular conditions such as erectile dysfunction, atherosclerosis, renal failure, hypertension, congestive heart failure, diabetic nephropathy, diabetic neuropathy, interstitial lung disease, obstructive sleep dyspnea, obstructive sleep apnea and resistant hypertension.

[031] Embodiments of the invention are also useful in treating cardiovascular disorders such as hypertension, pulmonary hypertension, postischemic renal failure, vasospasm, cerebral and cardiac ischemia, myocardial infarction, endotoxic shock, benign prostatic hyperplasia, complications of diabetes, migraine, bone resorption and inflammatory diseases, including Raynaud's disease and asthma. In one embodiment, the condition treated according to the invention is pulmonary arterial hypertension.

[032] Methods of the invention include dual drug tablets comprising both an ET_A antagonist and a PDE5 inhibitor. However, the two drugs may be provided in separate dosage formulations so that each may be administered substantially concurrently or at sequentially to provide required therapeutic amounts.

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[033] Improvement among a subject group may be measured through any number of ways known by those of ordinary skill in the art.

[034] The present invention will now be described in more detail with reference to exemplary embodiments thereof as shown in the accompanying drawings. While the present invention is described below with reference to exemplary embodiments, it should be understood that the present invention is not limited thereto. Those of ordinary skill in the art will recognize additional implementations, modifications and embodiments that are within the scope of the present invention, as well as other fields of use that may be of significance, in view of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[035] In order to facilitate a fuller understanding of the present invention, reference is now made to the accompanying drawings. These drawings should not be construed as limiting the present invention, but are intended to be exemplary only.

[036] Figure 1 is a depiction of ABT-627 (artrasentan), an ET_A-selective inhibitor.

[037] Figure 2 is a depiction of ABT-546, an ET_A-selective inhibitor.

[038] Figure 3 depicts sitaxsentan.

[039] Figure 4 depicts N-Oxazole thiophene sulfonamides described in Wu, et al., Recently discovered sulfonamide-, acyl sulfonamide- and carboxylic acid-based endothelin antagonists, Drugs, 6(3):232-239 (2003).

[040] Figure 5 depicts mean plasma concentrations of sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects following 100 mg doses of sitaxsentan or placebo daily for seven days.

[041] Figure 6 depicts mean plasma concentrations of N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects following 100 mg doses of sitaxsentan or placebo daily for seven days.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[042] All publications, patents and patent applications cited in this specification are hereby incorporated by reference as if each individual publication, patent or patent application were specifically and individually indicated to be incorporated by reference. Although the present invention is described in some detail by way of illustrations and examples for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art that certain changes and modifications may be made thereto

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without departing from the spirit or scope of the appended claims in view of the teachings of the present invention.

[043] "Pulmonary hypertension" is a specific condition of hypertension in the lung and relates to arterial hypertension, capillary hypertension or venous hypertension in the lung. The term "pulmonary hypertension" relates to pulmonary arterial hypertension (PAH). Furthermore it will be understood that pulmonary arterial hypertension relates to, but is not restricted to, both primary arterial hypertension and to pulmonary arterial hypertension occurring secondary to pulmonary diseases such as chronic bronchitis, emphysema, kyphoscoliosis and conditions such as chronic mountain sickness. Pulmonary hypertension is a serious medical condition that may lead to right ventricular hypertrophy, failure and death. When used herein the term "right heart failure" relates to disorders such as cor pulmonale and congenital abnormalities of the heart. It will be appreciated that cor pulmonale often occurs secondary to certain lung diseases such as chronic bronchitis and emphysema. Congenital abnormalities of the heart include disorders such as atrial septal defect, tetralogy of fallot, venticular septal defect and persistent ductus arteriosus.

Phosphodiesterase Inhibitors

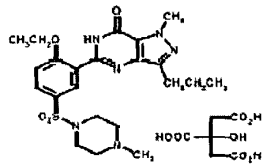
[044] One phosphodiesterase type 5 (PDE5) inhibitor, sildenafil (REVATIO), has recently been approved for treating PAH in 20 mg doses (TID). PDE5 is the main phosphodiesterase in the pulmonary vasculature; inhibiting it maintains high levels of cGMP, which promotes the vasodilating effects of endogenous nitric oxide (M Humbert and G Simonneau, Am. J. Respir. Crit. Care Med., 169:6 (2004)).

[045] However, PDE5s, such as sildenafil, have several adverse effects. For instance, in intermittent use of sildenafil (VIAGRA) for erectile dysfunction, once-daily doses of 25-100 mg has caused headaches, dyspepsia and visual disturbances. Its most serious effect has been severe, sometimes fatal, hypotension in patients taking nitrates for angina pectoris (*see*, Abramowicz, ed., Sildenafil for Pulmonary Hypertension, The Medical Letter on Drugs and Therapeutics, Vol. 46, Issue 1177, (March 1, 2004). The side effects are also present when using REVATIO to treat PAH. Therefore, it would be beneficial to combine a PDE5 inhibitor with an ET_A antagonist to provide complimentary treatment and reduce dosage amounts and/or side effects related to treatment with PDE5 inhibitors.

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[046] For each of the recited embodiments, useful phosphodiesterase type 5 inhibitors include, *e.g.*, vardenafil (LEVITRA), tadalafil (CIALIS), zaprinast, MBCQ, MY-5445, dipyridamole, furoyl and benzofuroyl pyrroloquinolones, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride (T-0156) and T-1032 (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth-oxy-phenyl)-3-isoquinoline carboxylate sulfate), and sildenafil. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385 and NM-702. Additional PDE5 inhibitors and their structures are described, for instance, in U.S. Patent No. 5,250,534 and U.S. Patent No. 6,469,012. Other forms of the PDE5 inhibitor, such as isomers (*e.g.* resolved enantiomers or racemic mixtures), metabolites, polymorphs, salts and complexes thereof, may also be used in an embodiment of the invention.

[047] In one embodiment, mixtures of the aforementioned PDE5 inhibitors is used. In another embodiment, the PDE5 inhibitor is tadalafil. In yet another embodiment, the PDE5 inhibitor is sildenafil. Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Endothelin Receptor Antagonists

[048] Because endothelin is associated with certain disease states and is implicated in numerous physiological effects, compounds that can interfere with or hinder endothelin-associated activities, such as endothelin-receptor interaction and vasoconstrictor activity, are of interest. Several compounds that are endothelin receptor antagonists have been identified. For example, a fermentation product of *Streptomyces misakiensis*, designated BE-18257B, has been identified as an ET_A antagonist. BE-18257B is a cyclic pentapeptide (cyclo(D-Glu-L-Ala-allo-D-Ile-L-Leu-D-Trp)), which

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inhibits ^{125}I-labeled endothelin-1 binding in cardiovascular tissues in a concentration-dependent manner (IC_{50} 1.4 μM in aortic smooth muscle, 0.8 μM in ventricle membranes and 0.5 μM in cultured aortic smooth muscle cells) but fails to inhibit binding to receptors in tissues in which ET_B predominates at concentrations up to 100 μM. Cyclic pentapeptides related to BE-18257B, such as BQ-123 (cyclo(D-Asp-Pro-D-Val-Leu-D-Trp)), have been synthesized and have also been shown to be ET_A antagonists (*see*, U.S. Pat. No. 5,114,918 to Ishikawa et al.; *see*, also, EP A1 0 436 189 to Banyu Pharmaceutical Co., Ltd (Oct. 7, 1991)). Studies that measure the inhibition by these cyclic peptides of endothelin-1 binding to endothelin-specific receptors indicate that these cyclic peptides bind preferentially to ET_A. Other peptide and non-peptidic ET_A antagonists have been identified (*see*, *e.g.*, U.S. Pat. Nos. 5,352,800; 5,334,598; 5,352,659; 5,248,807; 5,240,910; 5,198,548; 5,187,195 and 5,082,838). These include other cyclic peptides, acyltripeptides, hexapeptide analogs, certain anthraquinone derivatives, indanecarboxylic acids, certain N-pyrimidinylbenzenesulfonamides, certain benzenesulfonamides, and certain naphthalenesulfonamides (Nakajima et al., J. Antibiot., 44:1348-1356 (1991); Miyata et al., J. Antibiot., 45:74-78(1992); Ishikawa et al., J. Med. Chem., 35:2139-2142 (1992); U.S. Pat. No. 5,114,918 to Ishikawa et al.; EP A1 0 569 193; EP A1 0 558 258; EP A1 0 436 189 to Banyu Pharmaceutical Co., Ltd (Oct. 7, 1991); Canadian Patent Application No. 2,067,288; Canadian Patent Application No. 2,071,193; U.S. Pat. No. 5,208,243; U.S. Pat. No. 5,270,313; Cody et al., Med. Chem. Res., 3:154-162 (1993); Miyata et al., J. Antibiot., 45:1041-1046 (1992); Miyata et al., J. Antibiot., 45:1029-1040 (1992); Fujimoto et al., FEBS Letters, 305:41-44 (1992); Oshashi et al., J. Antibiot., 45:1684-1685 (2002); EP A1 0 496 452; Clozel et al., Nature, 365:759-761 (1993); International Patent Application No. WO 93/08799; Nishikibe et al., Life Sci., 52:717-724 (1993); and Benigni et al., Kidney Int., 44:440-444 (1993)). In general, the identified compounds have ET_A antagonist activity in *in vitro* assays at concentrations on the order of about 50-100 mM or less. A number of such compounds have also been shown to possess activity in *in vivo* animal models.

[049] It has been recognized that compounds that exhibit activity at IC_{50} or EC_{50} concentrations on the order of 10^{-4} mM or lower in standard *in vitro* assays that assess endothelin antagonist or agonist activity have pharmacological utility (*see*, *e.g.*, U.S.

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Pat. Nos. 5,352,800; 5,334,598; 5,352,659; 5,248,807; 5,240,910; 5,198,548; 5,187,195 and 5,082,838). By virtue of this activity, such compounds are considered to be useful for the treatment of hypertension such as peripheral circulatory failure, heart disease such as angina pectoris, cardiomyopathy, arteriosclerosis, myocardial infarction, pulmonary hypertension, vasospasm, vascular restenosis, Raynaud's disease, cerebral stroke such as cerebral arterial spasm, cerebral ischemia, late phase cerebral spasm after subarachnoid hemorrhage, asthma, bronchoconstriction, renal failure, particularly post-ischemic renal failure, cyclosporine nephrotoxicity such as acute renal failure, colitis, as well as other inflammatory diseases, endotoxic shock caused by or associated with endothelin and other diseases in which endothelin has been implicated.

[050] Therefore, compounds showing endothelin receptor antagonistic activity have prophylactic and therapeutic effects against diseases caused by ischemia, for example, cerebral infarction, angina pectoris, myocardial infarction and renal insufficiency.

[051] Thus, in view of the association of endothelin with numerous diseases, endothelin is believed to play a critical role in these pathophysiological conditions (*see*, Saito et al., Hypertension 15:734-738 (1990); Tomita et al., N. Engl. J. Med., 321: 1127 (1989) ; Kurihara et al., J. Cardiovasc. Pharmacol. 13(Suppl. 5):S13-S17 (1989); Doherty, J. Med. Chem. 35:1493-1508 (1992); Morel et al., Eur. J. Pharmacol., 167:427-428 (1989)).

[052] Accordingly, substances that specifically inhibit the binding of endothelin to its receptor (i.e. antagonists) should prevent the various above-mentioned physiological effects of endothelin and therefore, be valuable drugs. For example, endothelin receptor antagonists of the present invention can be used for the treatment of hypertension, pulmonary hypertension, myocardial infarction, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, hypertension or kidney failure caused by ischemia or intoxication as described in International Application Nos. WO96/11914 and WO95/26716.

[053] Two types of mammalian endothelin (ET) receptors, ET_A and ET_B, have been characterized. ET_A is selective for ET-1 and ET-2, while ET_B binds ET-1, ET-2 and

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ET-3 with equal affinity. ET_A mediates vasoconstriction and cell proliferation, whereas ET_B is important for the clearance of ET-1, endothelial cell survival, the release of nitric oxide and prostacyclin, and the inhibition of ECE-1 (*see*, Luscher, T. et al., Endothelins and Endothelin Receptor Antagonists, Therapeutic Considerations for a Novel Class of Cardiovascular Drugs, Circulation, 2434-2444 (November 7, 2000); Wu-Wong, et al, Pharmacology of endothelin receptor antagoinists ABT-627, ABT-546, A-182086 and A-192621: in vitro studies, Clinical Science, Suppl. 48, 107-111 (2002)).

[054] A major advance was made in the ET field with the development of endothelin receptor antagoinists. BQ-123 and FR139317, two peptidic ET_A-selective antagonists, are important advancements in the investigation of ET-mediated pathophysiology. Following the peptidic compounds, a number of nonpeptide antagonists with improved pharmacokinetics, such as Ro 47-0203, SB 217242, atrasentan, etc., were developed.

[055] Examples of endothelin receptor antagonists include, but are not limited to, BE 1827, BQ-610, ABT 627 (*see* Figure 1), ABT 546 (*see* Figure 2), Ro 61-1790, ZD1611, BMS-182874, BMS-193884, sitaxsentan (TBC 11251) (*see* Figure 3), EMD 122946, J-104132, LU 127043, LU 135252, SB 234551, SB 247083, and their derivatives, etc. (*see*, Doherty, Annual Reports in Medicinal Chemistry, 35:73-82 (Academic Press, 2000)). Other ethenesulfonamide derivatives, which are endothelin receptor antagonists and are useful in the methods of the present invention, are disclosed by Harada, et al., Chem. Pharm. Bull., 49(12):1593-1603 (2001). N-Oxazole thiophene sulfonamides (*see* Figure 4) are described in Wu, et al., Recently discovered sulfonamide-, acyl sulfonamide- and carboxylic acid-based endothelin antagonists, Drugs, 6(3):232-239 (2003)Other ET_A antagonists are described, for instance, in U.S. Patent Application Publication Nos. 20030092757 and 20030040534. Other forms of the ET_A antagonist, such as isomers (*e.g.* resolved enantiomers or racemic mixtures), metabolites, polymorphs, salts and complexes thereof, may also be used in an embodiment of the invention.

[056] In one embodiment, the ET_A antagonist is sitaxsentan, which is commercially marketed under the trademark THELIN. U.S. Patent Nos. 5,591,761; 5,594,021; 5,962,490; 6,248,767 and 6,458,805 disclose compositions including sitaxsentan,

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methods of using sitaxsentan and pharmaceutical compositions comprising sitaxsentan. U.S. Patent No. 5,783,705 discloses methods of making sitaxsentan.

[057] THELIN (sitaxsentan sodium; TBC11251Na) is an orally active endothelin A receptor antagonist that has been developed to treat pulmonary arterial hypertension (PAH). ET-1, produced primarily by vascular endothelial cells, is the predominant isoform found within the cardiovascular system and is a potent endogenous vasoconstrictor with proliferative and profibrotic effects. ET-1 also influences salt and water homeostasis as well as the renin-angiotensin-aldosterone and sympathetic nervous systems. There is a substantial body of experimental work suggesting that the primary physiologic effects of ET-1 in experimental animals and patients with PAH are sustained vasoconstriction of the pulmonary vasculature with remodeling due to proliferation or hypertrophy of vascular smooth muscle.

[058] Within the cardiovascular system, the effects of ET-1 on vascular smooth muscle cells and cardiac myocytes are believed to be principally mediated through the ET_A. Activation of ET_A facilitates sustained vasoconstriction of vascular smooth muscle, stimulation of, proliferation of, and hypertrophy of vascular smooth muscle cells, positive inotropic activity, and hypertrophy of cardiac cells. In contrast, ET_B is found primarily on endothelial cells, kidney, and central nervous tissue and are involved in the clearance of ET-1, particularly in the vascular beds of the lung and kidney. Endothelial ET_B facilitates vasodilation due to the release of smooth muscle relaxants such as nitric oxide and prostacyclin. Important stimuli for the release of ET-1 include, but are not limited to, hypoxia, ischemia, catecholamines, and angiotensin II. THELIN has a high specificity for ET_A, being approximately 6,500-fold more selective as an antagonist for ET_A compared to ET_B.

[059] Selective compounds for ET_A antagonists according to this invention, in general, should display a relative receptor binding ratio of at least 100, such as more than 1000, such as in increments of 500 greater than 1000, i.e. 1500, 2000, 2500, etc., if they are going to act at only one of the receptor subtypes, *e.g.* ET_A.

[060] Based upon the *in vitro* receptor affinity ratios, bosentan, which is the only endothelin receptor antagonist approved for the treatment of PAH, has an ET_A:ET_B selectivity ratio of 20 and is classified as a nonselective antagonist. In contrast, sitaxsentan has an ET_A:ET_B selectivity ratio of 6500 and is classified as an ET_A-

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selective antagonist. Therefore, for the purposes of this invention, bosentan or any other non-specific endothelin receptor antagonist would not represent an ET_A-specific antagonist.

[061] THELIN is a small molecule that blocks the action of endothelin, a potent mediator of blood vessel constriction and growth of smooth muscle in vascular walls. Endothelin receptor antagonists are effective in the treatment of a variety of diseases where the regulation of vascular constriction is important. Side effects of THELIN include liver dysfunction (increased ALT and AST), headache, edema, constipation, nasal congestion and flushing.

[062] Since ET_A appears to be selective for endothelin-1, examples of compounds that may be useful include, for instance, compounds described in U.S. Patent No. 5,686,478 and Table 1.

Table 1. Endothelin Antagonists

Compound	Target	Company	Indication/Comments
12m	ET_A	Rhone-Poulenc Rorer	Cardiovascular diseases
A-127772	ET_A	Abbott	
ABT-627	ET_A	Abbott	CHF; prostate cancer
BE-18572A/B	ET_A	Banyu	
BMS-20794	ET_A	Bristol Myers Squibb	
BMS-182874	ET_A	Bristol Myers Squibb	CHF
BMS-193884	ET_A	Bristol Myers Squibb	
BQ-123	ET_A	Banyu	Intravenous use only
BQ-153	ET_A	Banyu	Intravenous use only
BQ-162	ET_A	Banyu	Intravenous use only
BQ-485	ET_A	Banyu	Intravenous use only
BQ-610	ET_A	Banyu	Intravenous use only
EMD-122946	ET_A	Merck	CHF; hypertension
EMD-94246	ET_A	Merck	CHF; hypertension
FR-139317	ET_A	Fujisawa Pharm. Co.	
J-104121	ET_A	Merck/Banyu	
J-104132	ET_A	Merck/Banyu	Hypertension
L-744453	ET_A	Merck	Cardiovascular diseases
L-749329	ET_A	Merck	
L-754142	ET_A	Merck	

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Compound	Target	Company	Indication/Comments
LU127043	ET_A	Knoll	
LU135252	ET_A	Knoll	CHF; hypertension (darusentan)
LU208075	ET_A	Knoll	CHF; hypertension
LU302146	ET_A	Knoll	Occlusive vascular disease
PD-147953	ET_A	Parke-Davis	Cardiovascular diseases
PD-151242	ET_A	Parke-Davis	Cardiovascular diseases
PD-155080	ET_A	Parke-Davis	Cardiovascular diseases
PD-156707	ET_A	Parke-Davis	Cardiovascular diseases
RO 61-1790	ET_A	Hoffmann-La Roche	SAH; intravenous use only
S-0139	ET_A	Shionogi	Cardiovascular diseases
SB-234551	ET_A	SmithKline Beecham	
SB-247083	ET_A	SmithKline Beecham	
TA-0115	ET_A	Tanabe Seiyaku Co., Ltd Heart failure	
TA-0201	ET_A	Tanabe Seiyaku Co., Ltd Heart failure	
TBC11251	ET_A	Texas Biotechnology Company	CHF; primary pulmonary hypertension
WS-7338B	ET_A	Fujisawa	
ZD 1611	ET_A	Zeneca	Obstructive lung disease; primary pulmonary hypertension

Adapted from Luscher et al., Endothelins and Endothelin Receptor Antagonists: Therapeutic Considerations for a Novel Class of Cardiovascular Drugs, 2434-2340 at http://www.circulationaha.org.

[063] "ET_A antagonist" means any naturally occurring or synthetic compound that binds to the ET_A and blocks or inhibits the function of ET-1 or other agonist at that receptor. The ET_A antagonist may be a peptide or a non-peptide compound. Preferably, ET_A antagonists have a K_d for the ET_A of <1 μM, more preferably <100 nM, most preferably <10 nM, or even <1 nM. ET_A antagonists include, for example, sulfisoxazole, TBC-1 1251, BQ-123, BQ-610, BQ-745, PD 156707, PD 151242, TTA-386, JKC-301, JKC-302, BE-18257A, BE-18257B, A-1277722, LU 135252, TAK-044, SB 209670, SB 217242, FR139317, and ABT-627 (Table 2; Cheng et al., Ann. Reports in Medicinal Chemistry, Section II, Ch. 7, Endothelin Inhibitors, 61-70, (A. M. Doherty, ed., Academic Press, Inc. 1997).

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Table 2. Binding K_i (nM) to ET_A and ET_B for various ET receptor antagonists.

Compound	Company	ET_A	ET_B	Selectivity	Reference
ABT-627	Abbott	0.034	63.3	1862	[24]
ABT-546	Abbott	0.48	13,000	28,261	[23]
BMS-182874	Bristol-Myers Squibb	48	>50,000	>1000	[25]
FR-139317	Fujisawa	1.0	7300	7300	[12]
J-104132	Merck/Banyu	0.034	0.1	2.9	[26]
LU-135252	BASF/Knoll	1.4	184	130	[27]
PD-156707	Parke-Davis	0.17	139	818	[28]
Bosentan	Roche	6.5	343	53	[29]
Ro-61-1790	Roche	0.13	>130	1000	[30]
S-0139	Shionogi	1.0	1000	1000	[31]
SB-209670	SmithKline Beecham	0.20	18	90	[32]
SB-217242	SmithKline Beecham	1.1	111	101	[33]
T-0201	Tanabe	0.016	41	2700	[34]
TAK-044	Takeda	1.8	590	454	[35]
TBC-11251	Texas Biotechnology	0.43	>4300	10,000	[36]
ZD-1611	Zeneca	1.3*	>2000	1500	[37]

*K_i estimated from the IC_{∞} value (*see*, Wu-Wong, Endothelin Antagonists: Past, Present and Future, Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs, 1(3):346-351 (1999)).

[064] Some examples of ET receptor antagonists have undergone clinical development (*see* Table 3).

Table 3. ET receptor antagonists that have undergone clinical development.

Compound	Selectivity	Administration	Dev Phase	Indication
ABT-627	ET_A	po	II	Prostate cancer
BMS-182874	ET_A	iv	DX	CHF
BMS-193884	ET_A	po	I	CHF, pulmonary hypertension
FR-139317	ET_A	iv	DX	Hypertension, CHF, ischemia
J-104132/L-753037	ET_A/ET_B	po	I	Hypertension, CHF
LU-135252	ET_A/ET_B	po	II	CHF, other cardiovascular indications
Bosentan	ET_A/ET_B	po	III	CHF, hypertension, ischemia
Ro-48-5695	ET_A	po	II	CHF
Ro-61-0612	ET_A	po, iv	I	CHF, other cardiovascular
Ro-61-1790	ET_A	iv	I	ARF, SH
S-0139	ET_A	iv	I	Acute CHF, hypertension, CI
SB-209670	ET_A/ET_B	iv	II	ARF
SB-217242	ET_A/ET_B	po	II	COPD, urological
TAK-044	ET_A/ET_B	iv	II	MI, ARF, ACI, hepatoprotective
TBC-11251	ET_A	iv, po	IIa	CHF, COPD, hypertension, SH
ZD-1611	ET_A	po	I	CHF, pulmonary hypertension

ACI acute cerebral ischemia; ARF acute renal failure; COPD chronic obstructive pulmonary disease; CHF congestive heart failure; MI myocardial infarction; SH subarachnoid hemorrhage; DX discontinued

[065] For a discussion of the role of endothelin in hypertension see Krum, H. et al., Role of endothelin in hypertension and therapeutic potential of endothelin blockade, Cardiovascular, Pulmonary & Renal Investigational Drugs, 1(3):316-329 (1999). Table 4 outlines several biochemical and pharmacological properties of sitaxentan in comparison to bosentan.

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Table 4. Biochemical and pharmacological properties of sitaxsentan in comparison to bosentan.

Property	Sitaxsentan	Bosentan
Intrinsic potency to ET_A	Ki = 0.45 nM	Ki = 4.1 nM
$t_{1/2}$	10 hours	5 hours
Selectivity for ET_A:ET_B	6500	20
Effect on bile salt.	Does not accumulate bile salts.	Inhibits bile salt export pump, results in accumulation of bile salts in hepatocytes.
Effect on bilirubin.	No effect.	Has been shown to induce bilirubin accumulation in PAH patients.
Induction of cytochrome P450 enzymes.	No induction demonstrated to date clinically.	Causes inhibition, followed by induction of several CYP enzymes, including 3A4, 2C9, 2C19
Metabolism	Through 3A4 and 2C9	Through 3A4 and 2C9
Route of elimination	Mixed Hepatic and Renal	Hepatic

[066] For each of the recited embodiments, useful ET_A antagonists have been described above.

Combination Therapies

[067] The principle drawback for using sildenafil in treating PAH is that it requires a high dose three times a day (much higher than the dose for erectile dysfunction, which is 15 mg to 75 mg periodically). Currently, the only endothelin receptor antagonist which has been approved for use in PAH is bosentan, which is a nonselective compound that blocks both the A and the B receptors. Use of a nonselective ET receptor interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects.

[068] For instance, ET_A causes vasoconstriction, while ET_B causes vasodilatation. Bosentan works by blocking both ET_A and ET_B receptors. Sitaxsentan works by only blocking the ET_A and leaving the ET_B unimpaired. The mechanism by which ET_B causes vasodilatation is through stimulating the production of nitrous oxide and prostacylin. Nitrous oxide (NO) in turn activates the guanyl cyclase which increases

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the level of cGMP. The cGMP is responsible for relaxing the blood vessel. PDE5 acts to break down cGMP, so a PDE5 inhibitor also raises the level of cGMP, causing vasodilatation. Thus, when used together, increasing cGMP through the ET_B receptor and preventing its breakdown leads to increased vasodilatation and better efficacy of both drugs. Nonselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production. Additionally in a recent study, Bosentan, a non-selective antagonist, was tested with sildenafil, but the study was terminated due to pharmacokinetic drug interaction problems.

[069] Accordingly, the present invention relates to the use of a PDE5 inhibitor with an ET_A-specific antagonist therapy in inhibiting and preventing a cardiac stress or PAH. The methods and formulations of the invention provide new therapeutic approaches for the treatment and prevention of PAH in animals. "Treatment" or "treating" is also meant to encompass maintenance of cardiac conditions including PAH in a dormant (or quiescent) state at their primary site as well as secondary sites. Further, by "treating" or "treatment," it is meant to increase the efficacy as well as prevent or decrease resistance to therapeutic modalities. "Treating" or "treatment" is also meant to encompass prevention of recurrence, reduction of pain, discomfort, and disability (morbidity), and an increase in quality of life associated with the condition. By "increasing the efficacy", it is meant to include an increase in potency and/or activity of either the ET_A antagonist and/or the PDE5 inhibitor and/or a decrease in the required dosage. Status of patients receiving treatment may be evaluated by standards known in the art. For instance, a patient suffering from PAH may be subject to a 6 minute exercise walking test before and after the treatment period.

[070] A "therapeutically effective dose" refers to that amount of the active agents that results in achieving the desired effect. Toxicity and therapeutic efficacy of such active agents can be determined by standard pharmaceutical procedures in cell cultures or in experimental animals, *e.g.*, determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD_{50} and ED_{50}. A high therapeutic index is preferred. The data obtained from such data can be used in formulating a range of dosages for use in humans. The dosage of the active agents preferably lies within a range of circulating

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concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

[071] The exact formulation, route of administration, and dosage is determined by an individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide levels of the active agents that are sufficient to maintain therapeutic or prophylactic effects.

[072] The amount of pharmaceutical composition administered is dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. One embodiment of the invention contemplates the sequential administration of either the ET_A antagonist or the PDE5 inhibitor in separate daily dosages such that one may be given bi-daily while the other is provided once or three times a day. Likewise, sequentially is meant to include variations such as every other day treatment of agent and daily or multiple daily administrations of the other agent as required to achieve therapeutic effect. The combination therapy may be accomplished by providing the PDE5 inhibitor and the ET_A antagonist in separate dosage forms packaged together with instructions for the dosage administration regimen..

[073] It is greatly preferred that the PDE5 inhibitor and ET_A antagonist or a pharmaceutically acceptable salt thereof is administered in the form of a unit-dose composition, such as an oral unit dose for the treatment and/or prevention of the disorder, such as pulmonary hypertension.

[074] Daily amounts for PDE5 inhibitors will be in the range of 50 mg to 250 mg, which may be adjusted by increments of 5 mg, to encompass therapeutically useful ranges. For instance the range may be 50 mg to 225 mg, 50 mg to 215 mg, 50 mg to 200 mg, etc., or 55 mg to 250 mg, 60 mg to 250 mg, 65 mg to 250 mg, or 65 mg to 215 mg, 70 mg to 210 mg, etc. and variations thereof. Daily amounts for ET_A antagonists will be in the range of 5 mg to 125 mg, which may be adjusted by increments of 5 mg, to encompass therapeutically useful ranges. For instance the range may be 10 mg to 125 mg, 15 mg to 125 mg, 20 mg to 125 mg, etc., or 5 mg to 120 mg, 5 mg to 115 mg, 5 mg to 110 mg, or 25 mg to 90 mg, 30 mg to 85 mg etc. and variations thereof. Preferably the range of PDE5 inhibitor to ET_A antagonist in a ratio of 5:1 to 2:1.

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Formulation of Pharmaceutical Compositions

[075] The administration of any compound of this invention may be by any suitable means that results in a concentration of the compound that is effective for the treatment. The compound(s) may be contained in any appropriate amount in any suitable carrier substance, and is generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for the oral route. Thus, the composition(s) may be in the form of, *e.g.*, tablets, capsules, pills, powders, granulates, suspensions, emulsions, solution or gels. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (*see*, *e.g.*, Remington: The Science and Practice of Pharmacy (20th ed.), ed. A. R. Gennaro, Lippincott Williams & Wilkins, 2000 and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

[076] Pharmaceutical compositions according to the invention may be formulated to release the active compound (drug) substantially immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create a substantially constant concentration of the drug within the body over an extended period of time; (ii) formulations that, after a predetermined lag time, create a substantially constant concentration of the drug within the body over an extended period of time; (iii) formulations that sustain drug action during a predetermined time period by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance; (iv) formulations that localize drug action by, *e.g.*, spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ; and (v) formulations that target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type. Controlled release formulations may also release at least two active ingredients at different rates. In addition, controlled release formulations may release at least one active ingredient over various lengths of time, such as 12 hours or 24 hours. In one embodiment of the invention, the controlled release formulation releases at least one active ingredient over 24 hours.

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[077] Other embodiments of the invention include a pharmaceutical composition comprising an immediate release formulation and a controlled release formulation, wherein the immediate release formulation comprises an ET_A antagonist, a PDE5 inhibitor or both and the controlled release formulation comprises an ET_A antagonist, a PDE5 inhibitor or both. In one embodiment of the invention, the immediate release formulation comprises sitaxsentan and the controlled release formulation comprises sildenafil.

[078] Administration of compounds in the form of a controlled release formulation is especially preferred in cases in which the compounds in combination, have (i) a narrow therapeutic index (*i.e.*, the difference between the plasma concentration leading to harmful side effects or toxic reactions and the plasma concentration leading to a therapeutic effect is small); (ii) a narrow absorption window in the gastro-intestinal tract; or (iii) a very short biological half-life so that frequent dosing during a day is required in order to sustain the plasma level at a therapeutic level.

[079] Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, *e.g.*, various types of controlled release compositions and coatings. Thus, the drug is formulated with appropriate excipients in a pharmaceutical composition that, upon administration, releases the drug in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, patches, and liposomes.

Solid Dosage Forms For Oral Use

[080] Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (*e.g.*, sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (*e.g.*, cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (*e.g.*, sucrose, glucose, sorbitol, acacia,

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alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (*e.g.*, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

[081] The tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. The coating may be adapted to release the active drug substance in a predetermined pattern (*e.g.*, in order to achieve a controlled release formulation) or it may be adapted not to release the active drug substance until after passage of the stomach (enteric coating). The coating may be a sugar coating, a film coating (*e.g.*, based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (*e.g.*, based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose). Furthermore, a time delay material such as, *e.g.*, glyceryl monostearate or glyceryl distearate may be employed.

[082] The solid tablet compositions may include a coating adapted to protect the composition from unwanted chemical changes, (*e.g.*, chemical degradation prior to the release of the active drug substance). The coating may be applied on the solid dosage form in a similar manner as that described in Encyclopedia of Pharmaceutical Technology, *supra*.

[083] If more than one drug is administered simultaneously, the drugs may be mixed together in the tablet, or may be partitioned. In one example, a first drug is contained on the inside of the tablet, and a second drug is on the outside, such that a substantial portion of the second drug is released prior to the release of the first drug.

[084] Formulations for oral use may also be presented as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*,

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potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, *e.g.*, a mixer, a fluid bed apparatus or a spray drying equipment.

Controlled Release Oral Dosage Forms

[085] Controlled release compositions for oral use may, *e.g.*, be constructed to release the active drug by controlling the dissolution and/or the diffusion of the active drug substance. Controlled release formulations may also release at least two active ingredients at different rates.

[086] Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, *e.g.*, shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, *e.g.*, hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

[087] A controlled release composition containing one or more of the compounds of the claimed combinations may also be in the form of a buoyant tablet or capsule (*i.e.*, a tablet or capsule that, upon oral administration, floats on top of the gastric content for a certain period of time). A buoyant tablet formulation of the compound(s) can be prepared by granulating a mixture of the drug(s) with excipients and 20-75% w/w of hydrocolloids, such as hydroxyethylcellulose, hydroxypropylcellulose, or hydroxypropylmethylcellulose. The obtained granules can then be compressed into tablets. On contact with the gastric juice, the tablet forms a substantially water-

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impermeable gel barrier around its surface. This gel barrier takes part in maintaining a density of less than one, thereby allowing the tablet to remain buoyant in the gastric juice.

Liquids for Oral Administration

[088] Powders, dispersible powders, or granules suitable for preparation of an aqueous suspension by addition of water are convenient dosage forms for oral administration. Formulation as a suspension provides the active ingredient in a mixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents are, for example, naturally-occurring phosphatides (*e.g.*, lecithin or condensation products of ethylene oxide with a fatty acid, a long chain aliphatic alcohol, or a partial ester derived from fatty acids) and a hexitol or a hexitol anhydride (*e.g.*, polyoxyethylene stearate, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitan monooleate, and the like). Suitable suspending agents are, for example, sodium carboxymethylcellulose, methylcellulose, sodium alginate, and the like.

[089] Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents. Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

[090] Compositions for use in the treatment and/or prevention of pulmonary hypertension may be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of

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active compound suitably have diameters of less than 50 microns, preferably less than 10 microns, for example between 1 and 5 microns, such as between 2 and 5 microns. A favored inhaled dose will be in the range of about 0.05 mg to 2 mg, for example about 0.05 mg to 0.5 mg, about 0.1 mg to 1 mg or about 0.5 mg to 2 mg.

[091] As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

EXAMPLES

[092] The following examples present illustrative, but non-limiting, embodiments of the present disclosure.

EXAMPLE 1: Pharmacokinetic Drug Interaction Study

[093] A pharmacokinetic drug interaction study was performed using 24 individuals. In the study, a group of 24 normal, healthy volunteers participated in two treatment periods. During one treatment period, the subjects received 100 mg of sitaxsentan sodium (THELIN) for seven days and a single dose of 100 mg sildenafil (VIAGRA) on the last day. During the other treatment period, the subjects received placebo for seven days and 100 mg of VIAGRA on the seventh day. Twelve subjects were randomly assigned to each treatment period. When the subjects finished one treatment period, they were switched to the other treatment period. Two subjects (one in each group) did not complete the study.

[094] Each subject's blood was drawn, using EDTA as the anticoagulant, to determine plasma levels of sitaxsentan, sildenafil and N-desmethyl sildenafil. Samples were drawn (in duplicate) once on days 1, 3, 5 and 6; 15 times on day 7 and once again on day 8 for each treatment period. The samples were stored at a nominal temperature of -20°C for a duration not exceeding 38 days. All samples were analyzed with a set of calibration standards and low, medium and high concentration Quality Control samples.

[095] Results showed the sildenafil administration did not alter sitaxsentan levels. Table 5 summarizes the pharmacokinetic parameters for sildenafil and N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects after 100 mg of sitaxsentan or placebo daily for seven days in the presence of sitaxsentan The C_{max} (maximum concentration) of sildenafil increased by 18% and the AUC_{∞} (area under the plasma concentration/time curve) increased by 28%. No effects on levels of the active metabolite, N-desmethyl sildenafil, were observed. Table 6

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shows a statistical comparison of pharmacokinetic parameters for sildenafil and N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects after 100 mg of sitaxsentan or placebo daily for seven days.

[096] The mean plasma concentrations of sildenafil after oral administration of a single 100 mg doses of sildenafil to healthy subjects after a 100 mg dose of sitaxsentan or placebo daily for seven days are depicted in Figure 5, and the mean plasma concentrations of N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects after a 100 mg dose of sitaxsentan or placebo daily for seven days are depicted in Figure 6.

[097] Based on these data, VIAGRA does not appear to impact THELIN pharmacokinetics. THELIN showed a minor effect on overall VIAGRA pharmacokenetics, presumably based on the expected, weak, cytochrome P450 3A4 inhibition seen in cultured hepatocytes.

Table 5: Summary of pharmacokinetic parameters for sildenafil and N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects after 100 mg of sitaxsentan or placebo daily for seven days.

Parameter[1]	Sitaxsentan	Placebo
Sildenafil		
Cmax (ng/mL)	440 ± 232	377 ± 208
Tmax (h)	1.25	1.00
AUC_{0-t} (h•ng/mL)	1,575 ± 671	1,222 ± 474
AUC_{∞} (h•ng/mL)	1,648 ± 692	1,295 ± 488
λz (h^{-1})	0.2514 ± 0.0364	0.2584 ± 0.0444
t½ (h)	2.82 ± 0.45	2.76 ± 0.45
CL/F (mL/min)	147 ± 56.4	184 ± 69.0
Vz/F (L)	34.8 ± 11.5	43.6 ± 18.9
N-Desmethyl Sildenafil		
Cmax (ng/mL)	104 ± 40.8	109 ± 53.1
Tmax (h)	1.00	1.00
AUC_{0-t} (h•ng/mL)	389 ± 105	372 ± 107
AUC_{∞} (h•ng/mL)	425 ± 115	440 ± 112
λz (h^{-1})	0.1544 ± 0.0552	0.1506 ± 0.0569
t½ (h)	5.14 ± 2.13	05.1 ± 1.63
CL/F (mL/min)	529 ± 164	524 ± 234
Vz/F (L)	224 ± 76.4	217 ± 66.2

[1]Mean ± standard deviation except for Tmax, for which the median is reported.

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Table 6: Statistical comparison of pharmacokinetic parameters for sildenafil and N-desmethyl sildenafil after oral administration of a single 100 mg dose of sildenafil to healthy subjects after 100 mg of sitaxsentan or placebo daily for seven days.

Parameter	Ratio (%)[1] Estimate	90% Confidence Interval		
Sildenafil				
Cmax	117.61	93.81	→	147.46
AUC_{0-t}	124.95	113.40	→	137.68
AUC_{∞}	127.69	115.46	→	141.22
CL/F	80.03	72.63	→	88.18
Vz/F	81.50	70.98	→	93.59
N-Desmethyl Sildenafil				
Cmax	100.70	82.72	→	122.60
AUC_{0-t}	112.43	98.50	→	128.32
AUC_{∞}	105.78	96.21	→	116.30
CL/F	88.95	77.93	→	101.53
Vz/F	94.89	75.60	→	119.10

[1]GeomETic mean ratio. Based on analysis of natural log-transformed data.

Example 2: Efficacy Study

[098] A randomized, double-blind, placebo-controlled study is performed comprising 60 subjects who have moderate to severe pulmonary arterial hypertension resulting form one f the following conditions: idiopathic pulmonary arterial hypertension (PAH, also known as primary pulmonary hypertension); connective tissue disease (CTD); or congenital heart disease (CHD). The subjects are randomly assigned to one of the following dosage regimes (12 subjects per treatment):

(i) placebo and placebo;
(ii) placebo and 25 mg of THELIN;
(iii) placebo and 60 mg of sildenafil;
(iv) 25 mg of THELIN and 60 mg of sildenafil; and
(v) 50 mg of THELIN and 120 mg of sildenafil.

[099] Blood samples are collected to determine the level of THELIN in plasma and to assess sildenafil and N-desmethyl sildenafil pharmacokinetics and pharmacodynamics. Additionally, 6 minute walking distance tests are conducted to evaluate the change in the subjects' exercise capacity. Finally, symptoms of PAH are evaluated using NYHA/WHP functional class and rate of clinical worsening.

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[0100] Minimal drug interaction and side effects with treatment will occur in the combination THELIN and Sildenafil of groups (iv) and (v) while maintaining successful therapeutic effect.

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CLAIMS

1. A method of treating pulmonary hypertension comprising administering to a subject in need thereof an effective amount of a) a phosphodiesterase 5 (PDE5) inhibitor and b) an endothelin A receptor (ET_A) antagonist.

2. A method of reducing side effects or toxicity of an ET_A antagonist, a PDE5 inhibitor or both comprising administering a PDE5 inhibitor and an ET_A antagonist, wherein the amount of the PDE5 required to treat a condition is reduced or modulated.

3. A method of reducing side effects or toxicity of an ET_A antagonist, a PDE5 inhibitor or both comprising administering a PDE5 inhibitor and an ET_A antagonist, wherein the amount of the ET_A antagonist required to treat a condition is reduced or modulated.

4. A method of effecting or facilitating the treatment of a vascular condition in a mammal comprising administering a therapeutically effective amount of a) an ET_A antagonist and b) a PDE5 inhibitor.

5. A method for treating a vascular condition comprising administering to a subject in need thereof a therapeutically effective amount of a) an ET_A antagonist and b) a PDE5 inhibitor.

6. The method of any one of claims 1-5, wherein said ET_A antagonist is selected from the group consisting of from 12m, A-127772, A-1277722, ABT-627, BE 1827, BE-18257A, BE-18257B, BE-18572A/B, BMS-182874, BMS-193884, BMS-20794, BQ-123, BQ-153, BQ-162, BQ-485, BQ-610, BQ-745, EMD-122946, EMD-94246, FR-139317, J-104121, J-104132, JKC-301, JKC-302, L-744453, L-749329, L-754142, LU127043, LU135252, LU208075, LU302146, PD-147953, PD-151242, PD-155080, PD-156707, RO 61-1790, S-0139, SB 209670, SB 217242, SB-234551, SB-247083, sitaxsentan, sulfisoxazole, TA-0115, TA-0201, TAK-044, TBC11251, TTA-386, WS-7338B, ZD1611 and mixtures thereof.

7. The method of any one of claims 1-5 , wherein said phosphodiesterase 5 inhibitor is selected from the group consisting of vardenafil , tadalafil, zaprinast, dasantafil, MBCQ, MY-5445, dipyridamole, furoyl and benzofuroyl pyrroloquinolones, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester

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hydrochloride, T-1032 (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and mixtures thereof.

8. The method of any one of claims 1-5 , wherein the ET_A antagonist is selected from ABT-627, sitaxsentan, sulfisoxazole, TBC11251, ZD1611 and mixtures thereof.

9. The method of any one of claims 1-5 , wherein the PDE5 inhibitor is selected from vardenafil , tadalafil, dasantafil, dipyridamole, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride, (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, vesnarinone, zaprinast, and mixtures thereof.

10. The method of any one of claims 1-5 , wherein the ET_A antagonist is sitaxsentan

11. The method of any one of claims 1-5, wherein the PDE5 inhibitor is sildenafil.

12. The method of any one of claims 1-5, wherein the PDE5 inhibitor is tadalafil.

13. The method of any one of claims 1-5, wherein the ET_A antagonist is sitaxsentan and the PDE5 inhibitor is sildenafil.

14. The method of any one of claims 1-5, wherein the ET_A antagonist is sitaxsentan and the PDE5 inhibitor is tadalafil.

15. The method of claims 4 or 5, wherein said vascular condition is selected from the group consisting of erectile dysfunction, atherosclerosis, renal failure, hypertension, congestive heart failure, diabetic nephropathy, diabetic neuropathy, interstitial lung disease, obstructive sleep dyspnea, obstructive sleep apnea and resistant hypertension.

16. The method of claims 4 or 5, wherein said vascular condition is a cardiovascular condition.

17. The method of claim 15, wherein (a) and (b) are administered substantially concurrently.

18. The method of claim 15, wherein (a) and (b) are administered sequentially.

19. A combination therapy comprising at least one endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor.

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20. The combination therapy of claim 19, wherein said ET_A antagonist is selected from the group consisting of 12m, A-127772, A-1277722, ABT-627, BE 1827, BE-18257A, BE-18257B, BE-18572A/B, BMS-182874, BMS-193884, BMS-20794, BQ-123, BQ-153, BQ-162, BQ-485, BQ-610, BQ-745, EMD-122946, EMD-94246, FR-139317, J-104121, J-104132, JKC-301, JKC-302, L-744453, L-749329, L-754142, LU127043, LU135252, LU208075, LU302146, PD-147953, PD-151242, PD-155080, PD-156707, RO 61-1790, S-0139, SB 209670, SB 217242, SB-234551, SB-247083, sitaxsentan, sulfisoxazole, TA-0115, TA-0201, TAK-044, TBC11251, TTA-386, WS-7338B, ZD1611 and mixtures thereof.

21. The combination therapy of claim 19, wherein said PDE5 inhibitor is selected from the group consisting of vardenafil , tadalafil, dasantafil, MBCQ, MY-5445, dipyridamole, furoyl and benzofuroyl pyrroloquinolones, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride, T-1032 (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and mixtures thereof.

22. The combination therapy of claim 19, wherein the ET_A antagonist is selected from ABT-627, sitaxsentan, sulfisoxazole, TBC11251, ZD1611 and mixtures thereof.

23. The combination therapy of claim 19, wherein the PDE5 inhibitor is selected from vardenafil , tadalafil, dasantafil, dipyridamole, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride, (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, vesnarinone, zaprinast, and mixtures thereof.

24. The combination therapy of claim 19, wherein the ET_A antagonist is sitaxsentan

25. The combination therapy of claim 19, wherein the PDE5 inhibitor is sildenafil.

26. The combination therapy of claim 19, wherein the PDE5 inhibitor is tadalafil.

27. The combination therapy of claim 19, wherein the ETA antagonist is sitaxsentan and the PDE5 inhibitor is sildenafil.

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U.S. PATENT 8,268,847

28. The combination therapy of claim 19, wherein the ET_A antagonist is sitaxsentan and the PDE5 inhibitor is tadalafil.

29. The combination therapy of claim 19, wherein the ET_A antagonist and PDE5 inhibitor are administered together or separately.

30. The combination therapy of claim 19, wherein the combination therapy is a pharmaceutical composition.

31. The combination therapy of claim 19, wherein the pharmaceutical composition is in an immediate release formulation.

32. The combination therapy of claim 30, wherein the ET_A antagonist is in a controlled release formulation, the PDE5 inhibitor is in a controlled release formulation, or both are in a controlled release formulation.

33. The combination therapy of claim 30, wherein both the ET_A antagonist and the PDE5 inhibitor are in a controlled release formulation, but the ET_A antagonist and the PDE5 inhibitor are released at different rates.

34. A pharmaceutical composition comprising an ET_A antagonist, a PDE5 inhibitor and a pharmaceutical carrier.

35. The pharmaceutical composition of claim 34, wherein said ET_A antagonist is selected from the group consisting of 12m, A-127772, A-1277722, ABT-627, BE 1827, BE-18257A, BE-18257B, BE-18572A/B, BMS-182874, BMS-193884, BMS-20794, BQ-123, BQ-153, BQ-162, BQ-485, BQ-610, BQ-745, EMD-122946, EMD-94246, FR-139317, J-104121, J-104132, JKC-301, JKC-302, L-744453, L-749329, L-754142, LU127043, LU135252, LU208075, LU302146, PD-147953, PD-151242, PD-155080, PD-156707, RO 61-1790, S-0139, SB 209670, SB 217242, SB-234551, SB-247083, sitaxsentan, sulfisoxazole, TA-0115, TA-0201, TAK-044, TBC11251, TTA-386, WS-7338B, ZD1611 and mixtures thereof.

36. The pharmaceutical composition of claim 34, wherein said PDE5 inhibitor is selected from the group consisting of vardenafil , tadalafil, dasantafil, MBCQ, MY-5445, dipyridamole, furoyl and benzofuroyl pyrroloquinolones, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride, T-1032 (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, RX-RA-69, SCH-51866, KT-734,

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U.S. PATENT 8,268,847

vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and mixtures thereof.

37. The pharmaceutical composition of claim 34, wherein the ET_A antagonist is selected from ABT-627, sitaxsentan, sulfisoxazole, TBC11251, ZD1611 and mixtures thereof.

38. The pharmaceutical composition of claim 34, wherein the PDE5 inhibitor is selected from vardenafil , tadalafil, dasantafil, dipyridamole, 2-(2-Methylpyridin-4-yl)methyl-4-(3,4,5-trimethoxyphen- yl)-8-(pyrimidin-2-yl)methoxy-1,2-dihydro-1-oxo-2,7-naphthyridine-3-carbox- ylic acid methyl ester hydrochloride, (methyl 2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridylmethoxy)-4-(3,4,5-trimeth- oxy-phenyl)-3-isoquinoline carboxylate sulfate), sildenafil, vesnarinone, zaprinast, and mixtures thereof.

39. The pharmaceutical composition of claim 34, wherein the ET_A antagonist is sitaxsentan

40. The pharmaceutical composition of claim 34, wherein the PDE5 inhibitor is sildenafil.

41. The pharmaceutical composition of claim 34, wherein the PDE5 inhibitor is tadalafil.

42. The pharmaceutical composition of claim 34, wherein the ETA antagonist is sitaxsentan and the PDE5 inhibitor is sildenafil.

43. The pharmaceutical composition of claim 34, wherein the ET_A antagonist is sitaxsentan and the PDE5 inhibitor is tadalafil.

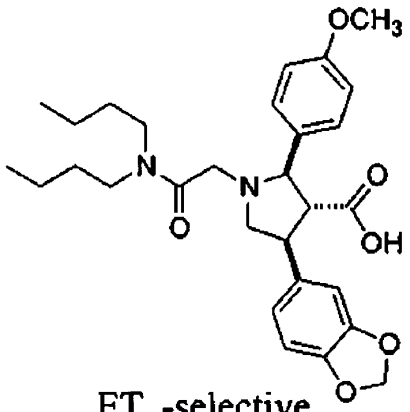
44. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition is in an immediate release formulation.

45. The pharmaceutical composition of claim 34, wherein the ET_A antagonist is in a controlled release formulation, the PDE5 inhibitor is in a controlled release formulation, or both are in a controlled release formulation.

46. The pharmaceutical composition of claim 34, wherein both the ET_A antagonist and the PDE5 inhibitor are in a controlled release formulation, but the ET_A antagonist and the PDE5 inhibitor are released at different rates.

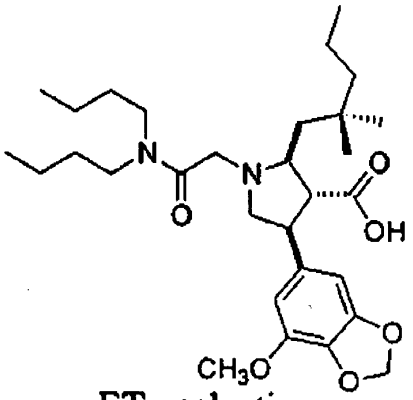
UNITED THERAPEUTICS CORP., EX1003, page 197
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U.S. PATENT 8,268,847

Figure 1



ET_A-selective
ABT-627

Figure 2



ET_A-selective
ABT-546

Figure 3

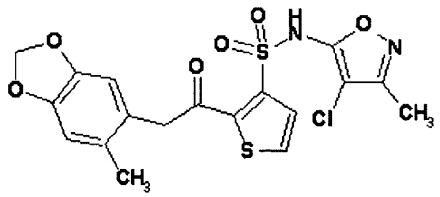


Figure 4

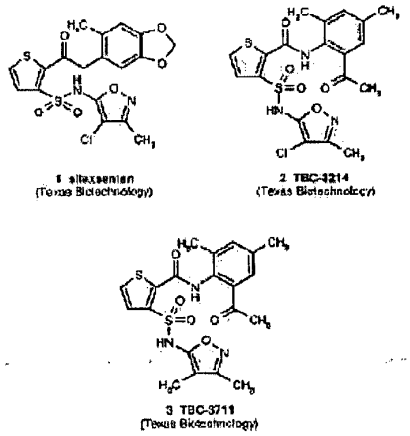

1 sitaxsentan
(Texas Biotechnology)
2 TBC-3214
(Texas Biotechnology)
3 TBC-3711
(Texas Biotechnology)

Figure 5

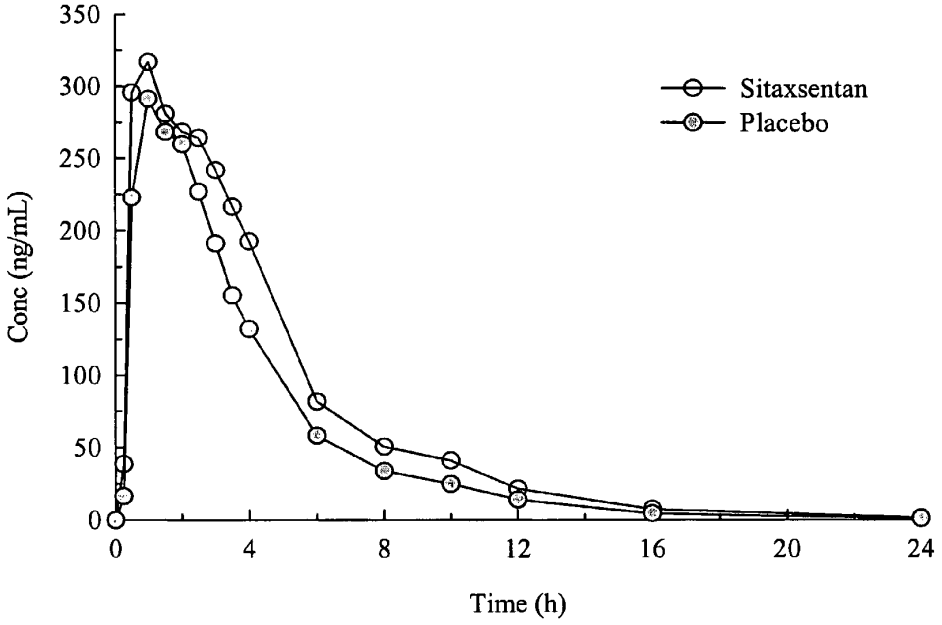

350
300
250
200
150
100
50
0
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
Sitaxsentan
Placebo

Figure 6

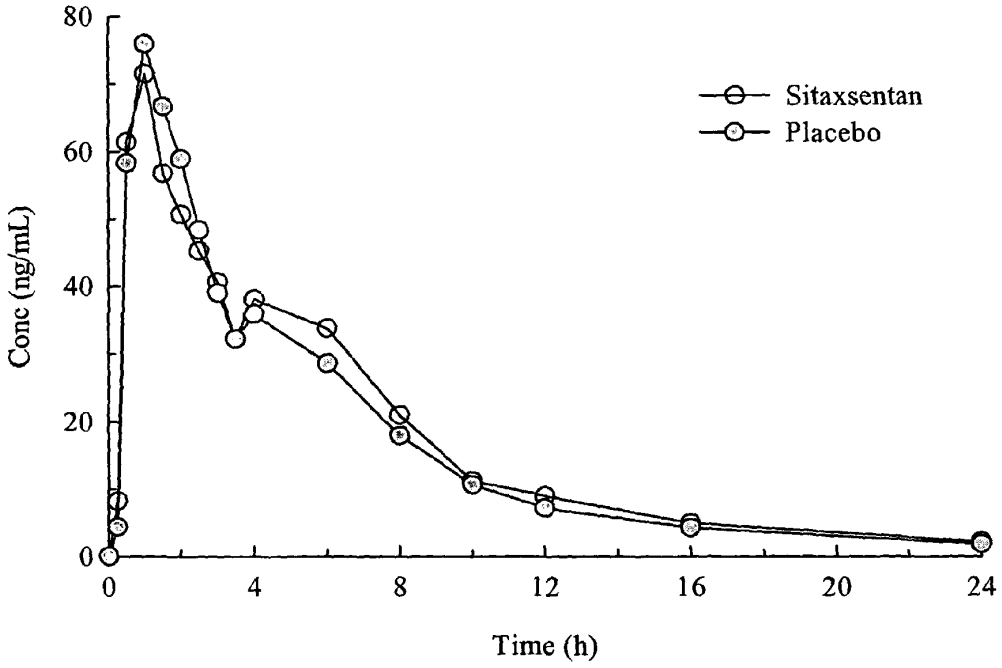

80
60
40
20
0
Conc (ng/mL)
0
4
8
12
16
20
24
Time (h)
Sitaxsentan
Placebo

EXHIBIT D

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/439,290	02/27/2009	Martine Clozel	AC-66-US	2770

50446 7590 02/28/2012

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MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
02/28/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/439,290	CLOZEL, MARTINE	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-12* is/are pending in the application.

5a) Of the above claim(s) *4 and 9-12* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3 and 5-8* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/27/12*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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U.S. PATENT 8,268,847

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of December 27, 2011 made to the office action filed September 27, 2011. Claims 1-12 are pending. Claims 4 and 9-12 are withdrawn in light of a restriction requirement filed June 1, 2011. The Applicant elected Group I, claims 1-9, taldalafil as the PDE5-inhibitor and pulmonary arterial hypertension as the disease in the reply filed on July 1, 2011. The Examiner would like to note that the claim identifier for claims 4 and 9 are incorrect. The claim identifier should be "(Withdrawn-Previously presented). For compact prosecution, the Examiner has withdrawn claims 4 and 9-12.

For the reasons in the previous office action and below, the Applicant's arguments of the obviousness-type double patenting rejections and 35 U.S.C. 103(a) rejection were found not persuasive, thus upheld.

Due to no new amendments to the claims, the previous rejections are repeated below. The Examiner has addressed the Applicant's arguments below.

Claims 1-3 and 5-8 are examined on the merits in regard to a composition. The use of the composition is not given patentable weight.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 1-3 and 5-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 7,094,781 ('781) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

The Patent '781 teaches the Applicant's compound.

The Patent '781 does not teach the composition with a PDE-5 inhibitor such as tadalafil.

Bolli et al. teach the Applicant's compound as an ET antagonist (see page 28, first row, right compound) in compositions that can be combined with an excipient and another active compound to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil are combined together to treat cardiac disorders such as hypertension (see abstract and claims 19 and 21).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor, because the compound of Formula I is a ET antagonist and Keyser et al. teach that ET antagonist and PDE5 inhibitors can be combined to treat hypertension.

2) Claims 1-3 and 5-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 12/388,142 ('142) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

This is a provisional obviousness-type double patenting rejection.

The Application '142 teaches a composition of formula I.

The Application '142 does not teach a combination with a PDE5 inhibitor such as tadalafil.

Bolli et al. teach the Applicant's compound as an ET antagonist (see page 28, first row, right compound) in compositions that can be combined with an excipient and another active compound to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil are combined together to treat cardiac disorders such as hypertension (see abstract and claims 19 and 21).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor, because the compound of Formula I is a ET antagonist and Keyser et al. teach that ET antagonist and PDE5 inhibitors can be combined to treat hypertension.

3) Claims 1-3 and 5-8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 12/066,448 ('448) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

This is a provisional obviousness-type double patenting rejection.

The Application ‘448 teaches a composition of formula I.

The Application ‘448 does not teach a combination with a PDE5 inhibitor such as tadalafil.

Bolli et al. teach the Applicant’s compound as an ET antagonist (see page 28, first row, right compound) in compositions that can be combined with an excipient and another active compound to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil are combined together to treat cardiac disorders such as hypertension (see abstract and claims 19 and 21).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor, because the compound of Formula I is a ET antagonist and Keyser et al. teach that ET antagonist and PDE5 inhibitors can be combined to treat hypertension.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-8 are rejected under 35 U.S.C. 103(a) as being obvious over Bolli et al. (WO 02/053557 A1) in view of Keyser et al. (WO 2006/026395 A1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing

that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Bolli et al. teach the Applicant's compound as an ET antagonist (see page 28, first row, right compound) in compositions that can be combined with an excipient and another active compound to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (see abstract and pages 16-17).

Bolli et al. does not teach a combination with at least one compound having PDE5 inhibitory properties such as tadalafil (Applicant's elected compound).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil are combined together to treat cardiac disorders such as hypertension (see abstract and claims 19 and 21).

To one skilled in the art it would be obvious and motivated to combine the compound of Formula I and a PDE5 inhibitor specifically tadalafil in a composition, because the compound of Formula I is a ET antagonist and Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil can be combined in a composition to treat hypertension.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

> The Applicant argues that in both the obviousness-type double patenting rejections and the 35 U.S.C 103(a) rejections, the Keyser et al. reference teaches away from the use of non-specific ET receptor antagonist, particularly those with ET_B antagonistic activities, in combination with a PDE5 inhibitor. As the compound of Formula I of the current invention is a dual ET_A/ET_B receptor antagonist, one skilled in the art would not be motivated to combine the teaching of any of the applications or WO 02/053557 to arrive at the claimed invention of the current application. For the reasons above, the restriction requirement is still traversed since the Examiner introduced the arguments for the first time. Applicants would like to not that the '781 patent is a national phase entry of WO 2006/026395

The Examiner disagrees because the Applicant's compound taught in Bolli et al. (see page 28, first row, right compound; also known as Example 104 seen on page 93, table 19) has a 682 relative receptor binding ratio for ET_A over ET_B (see page 6, example 104 wherein the IC50 for ET_A is 0.88 and 601 for ET_B) . According to Keyser et al. the selective compounds for ET_A antagonist according to the invention display a relative receptor binding ratio of at least 100 (see paragraph 59). Compared to bosentan which has a relative receptor binding ratio of 52, one would be motivated to use Applicant's compound. In addition, Applicant's compound falls within the range of "selective compounds for ET_A antagonist". Thus, the above argument applies to the obviousness-type double patenting rejections, 35 U.S.C. 103(a) rejection and the restriction.

In regards to WO 2006/026395 being used in the obviousness-type double patenting rejection, the WO document is used demonstrate in a published article that ET antagonist and PDE5 inhibitors such as tadalafil are combined together to treat cardiac disorders such as hypertension. Although patent '781 is the national stage phase entry of WO '395, the WO document can still be used because it is published art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KENDRA D CARTER
Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

EXHIBIT E

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC	5499

50446 7590 10/03/2016

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EXAMINER	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARTINE CLOZEL

Appeal 2014-009320
Application 13/604,148[1]
Technology Center 1600

Before LORA M. GREEN, FRANCISCO C. PRATS, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1–14 of U.S. Patent Application No. 13/604,148 ("the '148 application"). We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Appellants identify Actelion Pharmaceuticals Ltd. as the real party in interest. Appeal Br. 2.

STATEMENT OF THE CASE

Claims 1–14 are on appeal and stand rejected as unpatentable under 35 U.S.C. § 103(a) over Bolli[2] in view of Keyser[3]. Final Off. Act. 11. Claims 1–14 also stand rejected on the ground of non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781[4] in view of Bolli and Keyser. *Id*. at 3–5. The Examiner has also provisionally rejected claims 1–14 on the ground of non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142[5] in view of Bolli and Keyser, *id.* at 6–8, and over claims 1–11 of Clozel '847[6] in view of Bolli and Keyser, *id.* at 8–10.

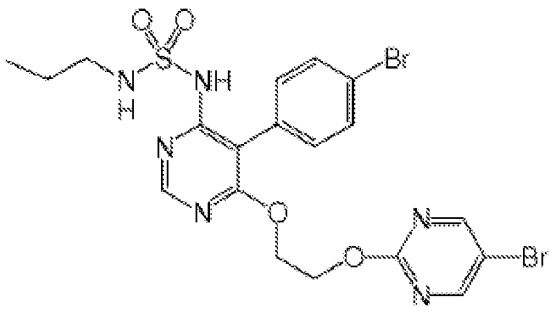
Claim 1 is illustrative of the claims on appeal. Claim 1 provides:

> 1. A method for the treatment of hypertension, pulmonary hypertension or pulmonary arterial hypertension, comprising administering simultaneously, separately or over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

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[2] Martin Bolli et al., WO 02/053557 A1 (published July 11, 2002) ("Bolli").
[3] Donald Keyser and Richard Dixon, WO 2006/026395 A1 (published March 9, 2006) ("Keyser").
[4] Martin Bolli et al., U.S. Patent No. 7,094,781 B2 (issued August 22, 2006) ("Bolli '781").
[5] Charles Tokunbo Adesuyi, U.S. Application No. 12/388,142 (filed Feb. 18, 2009) (issued as U.S. Patent No. 8,367,685 B2 on February 5, 2013) ("Adesuyi '142").
[6] Martine Clozel, U.S. Patent No. 8,268,847 B2 (issued September 18, 2012) ("Clozel '847").

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(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

Appeal Br. 12.

DISCUSSION

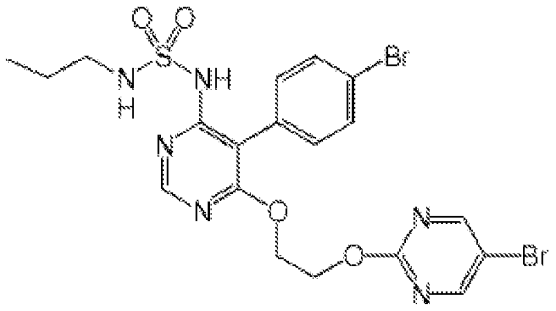
We have reviewed Appellant's arguments in the Briefs, the Examiner's Final Office Action, and the Examiner's Answer to the Appellant's arguments. Although we find that the Examiner made an adequate prima facie case of obviousness, we also find that the Examiner did not adequately respond to Appellant's argument that the claimed invention produces unexpectedly superior results. Thus, we reverse the rejection of claims 1–14 for obviousness over Bolli in view of Keyser, for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser. However, because the unexpectedly superior results do not apply to

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the Examiner's rejection of claims 1–11 of Clozel '847 in view of Bolli and Keyser, we affirm this rejection.

Background

The subject matter disclosed in the '148 application relates to a pharmaceutical product comprising the compound of formula (I):



(I)

in combination with at least one compound having PDE5[7]-inhibitory properties. Spec. 1. The Specification teaches that the compound of formula (I) is a known endothelin-receptor antagonist useful for the treatment of various diseases involving vasoconstriction (e.g., heart failure, angina pectoris, pulmonary and systemic hypertension, and erectile dysfunction). *Id.* In addition, the Specification teaches that pyrazolopyrimidinone derivatives (e.g., sildenafil, vardenafil, tadalafil, and udenafil) are known PDE5 inhibitors also useful for the treatment of the same vasoconstriction-related diseases. *Id.*

[7] PDE5 stands for cyclic guanosine 3', 5'-monophosphate (cGMP) phosphodiesterase type 5. Spec. 2.

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The Specification states that the claimed invention is based on the "surprising[]" finding "that the combination of the compound of formula (I) with a compound having PDE5-inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved." *Id.* at 2. In test Example 1, for example, the administration of a compound of formula (I) decreased blood pressure with an ABC ("area above the curve") of 256, and the administration of tadalafil decreased blood pressure with an ABC of 310. But, the administration of a combination of a compound of formula (I) and tadalafil decreased blood pressure with an ABC of 923, which the Specification describes as a "synergistic effect." *Id.* at 9; *see also id.* at 9–10 (Examples 2 and 3).

The Examiner rejected claims 1–14 for obviousness over Bolli in view of Keyser. Final Off. Act. 11. Bolli discloses pyrimidine-sulfamides of the general formula I. Bolli 12–14. Of those compounds, Bolli specifically discloses the compound of formula (I) presently claimed in the '148 application. *See id.* at 28 (top right-hand corner). Bolli teaches that the compounds act as endothelin-receptor antagonists, *id.* at 1, useful "for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin," such as hypertension and pulmonary hypertension, *id.* at 11. Moreover, Bolli teaches that the compounds of general formula I "may also be used in combination with one or more other therapeutically useful substances," such as α- and β-blockers, vasodilators, calcium-antagonists, ACE-inhibitors, potassium activators, angiotensin II receptor antagonists, diuretics, sympatholitics, "and other therapeutics which serve to treat high blood pressure or any cardiac disorders." *Id.* at 17.

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Bolli does not specifically teach that the "other therapeutics" may be PDE5 inhibitors. Final Off. Act. 12. The Examiner relied on Keyser to make up for this deficiency. Keyser discloses "combination therapies" comprising an endothelin A receptor (ET_A)[8] antagonist and a PDE5 inhibitor for the treatment and prevention of cardiac disorders such as pulmonary arterial hypertension. Keyser (Abstract). Keyser specifically identifies sildenafil, tadalafil, vardenafil, and dasantafil as PDE5 inhibitors. *Id.* ¶ 29. Keyser also lists several known peptide and nonpeptidic ET_A antagonists, including: "cyclic peptides, acyltripeptides, hexapeptide analogs, certain anthraquinone derivatives, indanecarboxylic acids, certain N-pyrimidinylbenzenesulfonamides, certain benzenesulfonamides, and certain naphthalenesulfonamides." *Id.* ¶ 48. Finally, Keyser teaches that the ET_A antagonist and PDE5 inhibitor may be administered together in a "dual drug tablet[]," or in "separate dosage formulations so that each may be administered substantially concurrently or [] sequentially to provide required therapeutic amounts." *Id.* ¶ 32.

Keyser does not identify the compound of formula (I) presently claimed in the '148 application. However, the Examiner argued that it would have been obvious to

> combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary arterial hypertension, because the compound of Formula I is a ET antagonist, and Keyser et al. teach that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be

[8] There are two types of endothelin receptors: endothelin A (ET_A) and endothelin B (ET_B). ET_A is predominant in cardiovascular tissues. Keyser ¶ 12.

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> combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

Final Off. Act. 13.

Analysis

A.

We agree with the Examiner that it would have been prima facie obvious to administer the compound of formula (I) as disclosed in Bolli and a PDE5 antagonist as taught by Keyser to treat hypertension.[9] Accordingly, we adopt the Examiner's fact findings and rationales provided in pages 11–13 of the Final Office Action. Where we disagree, however, is with the Examiner's treatment of Appellant's alleged unexpectedly superior results.

It is well established that "the prima facie case is merely a procedural device that enables an appropriate shift of the burden of production" from the examiner to the applicant. *Hyatt v. Dudas*, 492 F.3d 1365, 1369 (Fed. Cir. 2007). Here, the Appellant responds to the prima facie case with evidence of unexpectedly superior results. "After evidence or argument is

[9] For the sake of completeness, we note that Appellant's extensive "lead compound" arguments are inapposite to this case because the compound of formula (I) is not novel. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) ("We have held that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of adequate support in the prior art for the change in structure." (citations and quotations omitted)).

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submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Indeed, "[i]n reviewing the examiner's decision on appeal, the Board must necessarily weigh all of the evidence and argument." *Id.*

Upon reviewing the evidence of record, we find that Appellant submitted persuasive evidence of unexpectedly superior results that the Examiner did not adequately rebut. Specifically, Appellant found that the administration of the compound of formula (I) and a PDE5 antagonist decreased blood pressure in an amount much greater than either compound alone, thus producing a synergistic effect. Spec. 9–10 (Examples 1–3). In the case of synergistic effects, the "key question" as to obviousness is whether the combination of the compound of formula (I) and a PDE5 antagonist "proved more effective than what *would have been expected* in view of the prior art." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351–52 (Fed. Cir. 2013) (emphasis added). Here, the Examiner's response to Appellant's assertion of unexpected results consists of the following:

> With regard to the unexpected and synergistic results, the Examiner has considered the results and still does not find it persuasive to overcome the rejections of record because of the reasons above. Particularly, a combination of an ET antagonist and a PDE5 inhibitor is taught. There is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog (closest tested compound of art) taught by Bolli et al. for instance. Therefore the Applicant's arguments are non-persuasive to overcome the 35 U.S.C. 103(a) and obviousness type double patenting rejections of record.

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Ans. 14.

The Examiner refers to the N-ethyl analog of the compound of formula (I) disclosed in Bolli, and appears to imply that Appellant had a burden to test the effectiveness of that compound in combination with a PDE5 inhibitor. We disagree; the combination of the N-ethyl analog and a PDE5 inhibitor does not exist in the prior art. "It is not required that the claimed invention be compared with subject matter that does not exist in the prior art. The applicant is not required to create prior art, nor to prove that his invention would have been obvious if the prior art were different than it actually was." *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (Newman, J. concurring). Thus, we find that the Examiner has not persuasively showed by a preponderance of the evidence that Appellant's synergistic effects would have been expected from the prior art.

Moreover, we find that Appellant has presented persuasive evidence that an ordinarily skilled artisan would not have expected the synergistic effects produced by the administration of the compound of formula (I) and a PDE5 inhibitor. The compound of formula (I) is a dual ET_A-ET_B (i.e., nonselective) inhibitor. Appeal Br. 8–9. Keyser teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects." Keyser ¶ 67.

Specifically, Keyser explains that ET_A causes vasoconstriction. *Id.* at ¶ 68. Thus, administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension.

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ET_B, on the other hand, causes vasodilation. *Id.* ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP[10] levels. *Id.* cGMP relaxes blood vessels, but PDE5 breaks down cGMP. *Id.* Administration of a PDE5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE5 antagonist. *Id.* Conversely, Keyser explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production." *Id.*

Based on this description, we find that an ordinarily skilled artisan would not have expected the administration of a nonselective ET antagonist, such as the compound of formula (I), and a PDE5 antagonist to have produced the synergistic results provided in Appellant's Specification. If anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser. *See* Keyser ¶¶ 68–69. For these reasons, we determine that the Examiner's rejection of claims 1–14 for obviousness over Bolli in view of Keyser is unsupported by a preponderance of the evidence and therefore we reverse this rejection.

[10] cGMP stands for cyclic guanosine monophosphate.

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B.

For the same reasons, we also determine that the Examiner's rejections of claims 1–14 for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser, lack support by a preponderance of the evidence. Like Bolli, both Bolli '781 and Adesuyi '142 teach the compound of formula (I). But neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan. Thus, we reverse these non-statutory obviousness-type double patenting rejections.

C.

Finally, we affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. Clozel '847 teaches a method for treating hypertension or pulmonary hypertension by administering an effective amount of the compound of formula (I) in combination with a PDE5 inhibitory compound. *See, e.g.*, Clozel '847 (col. 8, ll. 29–35); *see also* Final Off. Act. 8–10. But, as Appellant notes, the '148 application is a continuation of the application leading to the '847 patent, Appeal Br. 11, and therefore is not prior art to the present application. We agree with the Examiner that a non-statutory obviousness-type double patenting rejection is appropriate in this case because representative claim 1 is not patentably distinct from the claims of

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Clozel '847. Specifically, representative claim 1 would be anticipated[11] by the claims of Clozel '847, but for the fact that Clozel '847 is not prior art. *In re Goodman*, 11 F.3d 1046, 1052–53 (Fed. Cir. 1993). Appellant makes no argument against the merits of this rejection. Therefore, we affirm.

SUMMARY

We affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. We reverse all other standing rejections.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

[11] Specifically, Clozel '847 discloses all elements of representative claim 1, except for the treatment of "pulmonary arterial hypertension." Final Off. Act. 8–9. But because representative claim 1 recites pulmonary arterial hypertension in the alternative (i.e., "the treatment of hypertension, pulmonary hypertension *or* pulmonary arterial hypertension"), Clozel '847 anticipates. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art.").

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Control Number(s)	
Filing Date(s)	Herewith
First Named Inventor	Martine Clozel
Title	Therapeutic Compositions Comprising a Specific Endothelin Receptor Ar
Patent Number	8,268,847
Examiner Name	
Attorney Docket No(s)	109693.000585

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I am the:
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OR
☒ Patent owner.
Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

Signature of Inventor or Patent Owner		Date	20 September 2017
Name	Frank Schaper / Eric Ruhlmann	Telephone	+41 61 565 6565
Title and Company	Chief Patent Counsel / Senior Patent Counsel, Actelion Pharmaceuticals Ltd		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Actelion Pharmaceuticals Ltd.

Application No./Patent No.: 8,268,847 Filed/Issue Date: 09-18-2012

Titled: THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

Actelion Pharmaceuticals Ltd., a limited company

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 028787, Frame 0964, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

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[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Joseph Lucci/	2017-09-22
Signature	Date
Joseph Lucci	33307
Printed or Typed Name	Title or Registration Number

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR
First Named Inventor/Applicant Name:	
Filer:	David N. Farsiou/Janis Calvo
Attorney Docket Number:	

Filed as Large Entity

Filing Fees for Supplemental Examination

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
REQUEST FOR SUPPLEMENTAL EXAMINATION	1826	1	4400	4400
REEXAM ORDERED BASED ON SUPP EXAM	1827	1	12100	12100
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**16500**

Electronic Acknowledgement Receipt	
EFS ID:	30442885
Application Number:	96000237
International Application Number:	
Confirmation Number:	5019
Title of Invention:	THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR
First Named Inventor/Applicant Name:	
Customer Number:	45511
Filer:	David N. Farsiou/Janis Calvo
Filer Authorized By:	David N. Farsiou
Attorney Docket Number:	
Receipt Date:	22-SEP-2017
Filing Date:	
Time Stamp:	09:58:58
Application Type:	Supplemental Examination
Patent Number:	8268847

Payment information:

Submitted with Payment	yes
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Payment was successfully received in RAM	$16500
RAM confirmation Number	092217INTEFSW00007674233050
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	1Transmittal_of_Request.pdf	168841 c7ae38e8f8c733ff384bbd60479691185a97504e	no	4
Warnings:					
Information:					
2	Receipt of Orig. Supp Exam Request	2Request_For_Supplemental_Examination.pdf	176507 5010fc57097ce6752061776dbf46964c7dd91852	no	14
Warnings:					
Information:					
3	Copy of patent for which supp exam is requested	3Exhibit_A.pdf	8139850 6640987d4ce0bf19f5afc23e4bc3f641b2663627	no	7
Warnings:					
Information:					
4	List of Items of Information - Supp Exam	4Exhibits_B_through_D.pdf	6049802 1724a620d21bb4d909a9812d7e96f4529a276156	no	197
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	5Exhibit_E.pdf	510439 07b133faed3fb0d642bd566ebdad86208fdcd885	no	14
Warnings:					
Information:					
6	Power of Attorney	6Power_of_Attorney_and_Change_of_Correspondence_Address.pdf	969247 0bd11cb0d617da3500b34eb882b11b27d36e0ca3	no	2
Warnings:					

Information:					
7	Assignee showing of ownership per 37 CFR 3.73	7Assignee_Statement_of_Ownership.pdf	75502 d3cb84e6f06f42a0e8712e7d60078ac87e06ed59	no	2
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	31342 22a638ca63ae3a87b952f74811cec82026c502c2	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	16121530	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/59 (09-16)
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REQUEST FOR SUPPLEMENTAL EXAMINATION TRANSMITTAL FORM

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Attorney Docket No.:

Date:

1. ☑ This is a request for supplemental examination pursuant to 37 CFR 1.610 of patent number 8,268,847 issued September 18, 2012. 37 CFR 1.610(b)(1).

2. ☑ Supplemental examination of claim(s) 1-11 is requested. 37 CFR 1.610(b)(4).

3. ☑ a. The name(s) of the patent owner(s) (**not** the patent practitioner(s)) is (are):
Actelion Pharmaceuticals Ltd

☑ b. A submission by the patent owner(s) in compliance with 37 CFR 3.73(c), which establishes that the patent owner(s) has (have) the entirety of the ownership in the patent for which supplemental examination is requested, is included. 37 CFR 1.610(b)(9).

4. ☐ a. A check in the amount of $_____ is enclosed to cover the fee for processing and treating a request for supplemental examination, the fee for reexamination ordered under 35 USC 257, and the fee for processing and treating each non-patent document over 20 sheets in length (37 CFR 1.20(k)(1 - 3));

☑ b. The Director is hereby authorized to charge all applicable fees as set forth in 37 CFR 1.20(k)(1 - 3) to Deposit Account No. 233050; or

☐ c. Payment by credit card. Form PTO-2038 is attached. 37 CFR 1.610(a).

5. ☑ Any refund should be made by ☐ check or ☑ credit to Deposit Account No. 233050. 37 CFR 1.26(c). If payment is made by credit card, refund must be to the credit card account.

6. ☑ A copy of the patent for which supplemental examination is requested, and a copy of any disclaimer or certificate issued for the patent are included. 37 CFR 1.610(b)(6).

7. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
☐ Landscape Table on CD

8. ☐ Nucleotide and/or Amino Acid Sequence Submission
If applicable, items a. – c. are required.

a. ☐ Computer Readable Form (CRF)
b. Specification Sequence Listing on:

i. ☐ CD-ROM (2 copies) or CD-R (2 copies); **or**
ii. ☐ paper

c. ☐ Statements verifying the identity of above copies

9. ☑ A list of no more than 12 items of information submitted as part of this request is provided in Part B of this form. Where appropriate, the list must meet the requirements of 37 CFR 1.98(b). 37 CFR 1.605(a), 1.610(b)(2).

This collection of information is required by 37 CFR 1.610. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 0.3 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

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10. ☑ A legible copy of each item of information listed in Part B of this form, and an English language translation of all necessary and pertinent parts of each non-English language item of information are included.

Copies of items of information that form part of the discussion within the body of the request (see 37 CFR 1.605(b)), and copies of U.S. patents and patent application publications, are not required. 37 CFR 1.610(b)(7).

11. ☐ A summary of the relevant portions of each non-patent document that is over 50 pages in length (other than the request) is included. The summary includes the required citations to the particular pages containing the relevant portions. 37 CFR 1.610(b)(8).

12. ☑ A separate, detailed explanation of the relevance and manner of applying each item of information to each claim of the patent for which supplemental examination is requested, is included. 37 CFR 1.610(b)(5).

13. ☐ The below list includes all prior or concurrent post-patent Office proceedings (*ex parte* or *inter partes* reexamination, reissue, supplemental examination, post grant review, or *inter partes* review) involving the patent for which supplemental examination is being requested. 37 CFR 1.610(b)(3). An identifying number may be, e.g., a control no. or reissue application no. Any prior or concurrent post-patent Office proceedings not listed below are listed on a separate paper accompanying the request.

Type of Proceeding	Identifying Number	Filing Date

☐ See accompanying paper for a list of additional prior or concurrent post-patent Office proceedings involving the patent for which supplemental examination is requested. The paper should be a separate sheet titled "List of Prior or Concurrent Post-Patent Office Proceedings" and must provide the type, identifying number, and filing date of the post-patent Office proceeding.

14. Correspondence Address: Please recognize, or change, the correspondence address for the file of the patent for which supplemental examination is requested **and** for the supplemental examination proceeding to be:

☑ The address associated with Customer Number: 45511 **OR**

☐ Firm or Individual Name

Address

City	State	Zip

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15. **WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

/Joseph Lucci/ — Authorized Signature

2017-09-22 — Date

Joseph Lucci — Typed/Printed Name

33307 — Registration No.

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REQUEST FOR SUPPLEMENTAL EXAMINATION TRANSMITTAL FORM
PART B – LIST OF ITEMS OF INFORMATION – Page 1

Patent number for which supplemental examination is requested 8,268,847 Issue Date 9/18/2012

All items of information (no more than 12) submitted herewith as part of this request for supplemental examination of the above-identified patent are included in the following list:

U. S. PATENT DOCUMENTS

Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	US- 7094781-B2	08/22/2006	Actelion Pharmaceuticals Ltd	See accompanying Request
	US- 8367685-B2	02/05/2013	Actelion Pharmaceuticals Ltd	See accompanying Request
	US-			
	US-			
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FOREIGN PATENT DOCUMENTS

Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[2]
Exh. B	WO-2002053557-A1	07/11/2002	Actelion Pharmaceuticals Ltd	See accompanying Request	
Exh. C	WO-2006026395-A1	03/09/2006	Encysive Pharmaceuticals	See accompanying Request	

[1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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(Also referred to as FORM PTO-XXXX)

REQUEST FOR SUPPLEMENTAL EXAMINATION TRANSMITTAL FORM
PART B – LIST OF ITEMS OF INFORMATION – Page 2

Patent number for which supplemental examination is requested 8,268,847 Issue Date 9/18/2012

All items of information (no more than 12) submitted herewith as part of this request for supplemental examination of the above- identified patent are included in the following list:

OTHER DOCUMENTS

Cite No.[1]	Document Information (include, where appropriate, name of the author, title of the article, book, magazine, journal, serial, symposium, catalog, etc., publication date, page(s), volume-issue number(s), publisher, city and/or country where published. If a court document, identify the specific court, the designation (case citation or numeric designation), the title of the document, and the date submitted in court. If a declaration, include the type (e.g., 37 CFR 1.132 or 1.131), name of declarant, and the date of declaration. If an invoice or sales receipt, include the date issued and the name of the issuer (e.g., the name of the corporation or other place of business). If a discussion within the body of the request, include the pages of the request on which the discussion appears, and a description of the discussion (e.g., "discussion in request of why the claims are patentable under 35 U.S.C. 101, pages 7-11.") For all other materials, include, where appropriate, the title, author, date, and any descriptive information that would describe the document.)	T[2]
Exh. D	Office Action mailed February 28, 2012 during prosecution of the '847 patent	

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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BIB DATA SHEET

CONFIRMATION NO. 5019

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
96/000,237	09/22/2017 RULE	514	3991	

APPLICANTS

INVENTORS

8268847, Residence Not Provided;
ACTELION PHARMACEUTICALS, LTD., ALLSCHWIL, SWITZERLAND;
PATENT OWNER, Residence Not Provided;

**** CONTINUING DATA ***************************

This application is a SER of 12/439,290 02/27/2009 PAT 8268847
which is a 371 of PCT/IB07/53448 08/28/2007

**** FOREIGN APPLICATIONS ***************************

INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/052999 08/29/2006
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/053857 10/19/2006

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

Foreign Priority claimed ☐ Yes ☐ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS

ADDRESS

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891
UNITED STATES

TITLE

THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

FILING FEE RECEIVED		
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Litigation Search Report CRU 3999

Reexam Control No. 96/000,237

TO: TIMOTHY KUGEL	From: MANUEL SALDANA
Location: CRU	Location: CRU 3999
Art Unit: 3991	MDE 5D14
Date: 09/25/2017	Phone: (571) 272-7740
	MANUEL.SALDANA@uspto.gov

Search Notes

Litigation was NOT found for US Patent Number: **8,268,847**

1) I performed a KeyCite Search in Westlaw, which retrieves all history on the patent including any litigation.

2) I performed a search on the patent in Lexis CourtLink for any open dockets or closed cases.

3) I performed a search in Lexis in the Federal Courts and Administrative Materials databases for any cases found.

4) I performed a search in Lexis in the IP Journal and Periodicals database for any articles on the patent.

5) I performed a search in Lexis in the news databases for any articles about the patent or any articles about litigation on this patent.

Patent Search 8268847 9/25/2017

No cases found.

Return to Search

(Charges for search still apply)

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1. 9597331, March 21, 2017, Therapeutic compositions containing macitentan, Clozel, Martine, Binningen, Swiss Confederation(CH); 873787, October 2, 2015, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:036718/0102, ACTELION PHARMACEUTICALS LTD., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, receptor, macitentan, salt, prostacyclin, agonist, pulmonary, pharmaceutically, rat, hypertension, therapeutic, monocrotaline, administered, ingredient, endothelin, arterial, disease, route, cell, hypertensive, experimental, isopropyl, formula, variant, butoxy, amino, dose, invention relates, arterial blood, analogues

... 2011, Bolli et al., United States of America (US) 8268847, September 18, 2012, Clozel et al., United ...

2. 9597331, March 21, 2017, Therapeutic compositions containing macitentan, Clozel, Martine, Binningen, Swiss Confederation(CH); 873787, October 2, 2015, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:036718/0102, ACTELION PHARMACEUTICALS LTD., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, receptor, macitentan, salt, prostacyclin, agonist, pulmonary, pharmaceutically, rat, hypertension, therapeutic, monocrotaline, administered, ingredient, endothelin, arterial, disease, route, cell, hypertensive, experimental, isopropyl, formula, variant, butoxy, amino, dose, invention relates, arterial blood, analogues

... 2011, Bolli et al., United States of America (US) 8268847, September 18, 2012, Clozel et al., United ...

3. 9265762, February 23, 2016, Stable pharmaceutical compositions comprising a pyrimidine-sulfamide, Adesuyi, Charles Tokunbo, Swindon, United Kingdom of Great Britain and Northern Ireland(GB); Lithgow, Bruce Hamilton, Bath, United Kingdom of Great Britain and Northern Ireland(GB); Lambert, Olivier, Spechbach-le-Haut, French Republic(FR); Holman, Lovelace, Arlesheim, Swiss Confederation(CH); 736699, January 7, 2016, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:037431/0969, ACTELION PHARMACEUTICALS LTD., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: formula, composition, pharmaceutical, compound, sodium, starch, tablet, total weight, coating, glycolate, stearate, magnesium, acid, total amount, disintegrant, minute, batch, dissolution, cellulose, pharmaceutically, sulphate, lauryl, microcrystalline, surfactant, percentage, lubricant, intra-granular, salt, notably, ensp

... 2011, Blouquin et al., United States of America (US) 8268847, September 18, 2012, Clozel, United States of America (US) ...

4. 9173881, November 3, 2015, Therapeutic compositions containing macitentan, Clozel, Martine, Binningen, Swiss Confederation(CH); 335657, October 20, 2014, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:033980/0325, ACTELION PHARMACEUTICALS LTD., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, receptor, macitentan, salt, prostacyclin, agonist, pulmonary, pharmaceutically, rat, hypertension, therapeutic, monocrotaline, administered, ingredient, endothelin, arterial, disease, route, cell, hypertensive, experimental, isopropyl, formula, variant, butoxy, amino, dose, invention relates, arterial blood, analogues

... 2011, Bolli et al., United States of America (US) 8268847, September 18, 2012, Clozel, United States of America (US) ...

5. 8809334, August 19, 2014, Therapeutic compositions containing macitentan, Clozel, Martine, Binningen, Swiss Confederation(CH); 058639, February 21, 2013, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:029850/0458, Actelion Pharmaceuticals Ltd., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, receptor, macitentan, salt, prostacyclin, agonist, pulmonary, pharmaceutically, rat, hypertension, therapeutic, monocrotaline, administered, ingredient, endothelin, arterial, disease, route, cell, hypertensive, experimental, isopropyl, formula, variant, butoxy, amino, dose, invention relates, arterial blood, analogues

... 2011, Bolli et al., United States of America (US) 8268847, September 18, 2012, Clozel et al., United ...

6. 8541433, September 24, 2013, Combination comprising macitentan and paclitaxel for treating multi-drug resistant ovarian cancer, Clozel, Martine, Binningen, Swiss Confederation(CH); Regenass, Urs, Allschwil, Swiss Confederation(CH); 867939, October 5, 2010, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16 CH 4123, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:025089/0838, Actelion Pharmaceuticals, Ltd., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: paclitaxel, compound, mice, formula, tumor, salt, cancer, pharmaceutically, ovarian, ascite, plusmn, formation, ensp, incidence, route, therapeutic, antagonist, ingredient, patient, i.p, pharmaceutical, experimental, endothelin, inhibition, suspension, receptor, assay, dose, administered, composition

... Bolli et al., United States of America (US), 514#235.8 8268847, September 18, 2012, Clozel et al., United ...

7. 8497370, July 30, 2013, Processes for preparing amine salts of sildenafil-analogues and use thereof, Chen, Ing-Jun, Kaohsiung, Taiwan, Republic of China (R.O.C.)(TW); 044899, March 10, 2011, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., KAOHSIUNG MEDICAL UNIVERSITY, SAN MING DISTRICT, NO. 100, SHIH-CHUAN 1ST RD., KAOHSIUNG CITY, TAIWAN( ), 807, reel-frame:025935/0662, Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China (R.O.C.)(TW), Foreign company or corporation

CORE TERMS: acid, sodium, salt, derivative, statin, g-polyglutamic, sildenafil-analogues, ethanol, amine, calcium, formula, plusmn, carboxylic, dissolved, compound, substituting, simvastatin, mixture, ester, room temperature, carrier, preparation, alkyl, composition, pharmaceutical, alcohol, pharmaceutically, pulmonary, hydroxide, donated

... 2009, Braude et al., United States of America (US) 8268847, September 18, 2012, Clozel, United States of America (US), ...

8. 8268847, September 18, 2012, Therapeutic compositions comprising a specific endothelin receptor antagonist and a PDE5 inhibitor, Clozel, Martine, Binningen, Swiss Confederation(CH), Swiss Confederation(); 439290, August 15, 2012, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:028787/0964, Actelion Pharmaceuticals, Ltd., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, formula, rat, hypertension, salt, blood pressure, pharmaceutically, tadalafil, administered, therapeutic, sildenafil, disease, pulmonary, route, dose, i.a, ingredient, tube, vasoconstriction, salt-sensitive, spontaneously, hypertensive, decreased, min, heart failure, protocol, mixture, resin, angina pectoris, dysfunction 8268847

9. 20140148460 (Note: This is a Patent Application only.), May 29, 2014, THERAPEUTIC COMPOSITIONS,

CLOZEL, Martine, Binnigen, Swiss Confederation(CH); 162280, April 15, 2014, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:032677/0102; April 17, 2014, CORRECTIVE ASSIGNMENT TO CORRECT THE CORRECT ATTORNEY DOCKET NUMBER TO "AC-66-USC2" PREVIOUSLY RECORDED ON REEL 032677 FRAME 0102. ASSIGNOR(S) HEREBY CONFIRMS THE ASSIGNMENT., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:032708/0012, ACTELION PHARMACEUTICALS LTD., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, formula, rat, hypertension, salt, blood pressure, pharmaceutically, tadalafil, administered, therapeutic, sildenafil, disease, pulmonary, i.a, route, dose, ingredient, tube, vasoconstriction, salt-sensitive, spontaneously, hypertensive, decreased, min, heart failure, protocol, mixture, resin, angina pectoris, dysfunction

... Ser. No. 12439290, February 27, 2009, GRANTED 8268847

10. 20130210830 (Note: This is a Patent Application only.), August 15, 2013, THERAPEUTIC COMPOSITIONS, CLOZEL, Martine, Binnigen, Swiss Confederation(CH); 604148, September 5, 2012, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:028901/0418, Actelion Pharmaceuticals Ltd., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, formula, rat, hypertension, salt, blood pressure, pharmaceutically, tadalafil, administered, therapeutic, sildenafil, disease, pulmonary, i.a, route, dose, ingredient, tube, vasoconstriction, salt-sensitive, spontaneously, hypertensive, decreased, min, heart failure, protocol, mixture, resin, angina pectoris, dysfunction

... Ser. No. 12439290, February 27, 2009, GRANTED 8268847
Prior Publication 20130005734, January 3, 2013

11. 20130005734 (Note: This is a Patent Application only.), January 3, 2013, THERAPEUTIC COMPOSITIONS, CLOZEL, Martine, Binnigen, Swiss Confederation(CH), Swiss Confederation(); 604148, September 5, 2012, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:028901/0418, Actelion Pharmaceuticals Ltd., Allschwil, Swiss Confederation(CH), Foreign company or corporation

CORE TERMS: compound, formula, rat, hypertension, salt, blood pressure, pharmaceutically, tadalafil, administered, therapeutic, sildenafil, disease, pulmonary, i.a, route, dose, ingredient, tube, vasoconstriction, salt-sensitive, spontaneously, hypertensive, decreased, min, heart failure, protocol, mixture, resin, angina pectoris, dysfunction

... Ser. No. 12439290, February 27, 2009, GRANTED 8268847

12. 20120108604 (Note: This is a Patent Application only.), May 3, 2012, PROCESSES FOR PREPARING AMINE SALTS OF SILDENAFIL-ANALOGUES AND USE THEREOF, Chen, Ing-Jun, Kaohsiung City, Taiwan, Province of China(TW), Taiwan, Province of China(); 044899, March 10, 2011, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., KAOHSIUNG MEDICAL UNIVERSITY, SAN MING DISTRICT, NO. 100, SHIH-CHUAN 1ST RD., KAOHSIUNG CITY, TAIWAN( ), 807, reel-frame:025935/0662, KAOHSIUNG MEDICAL UNIVERSITY, Kaohsiung City, Taiwan, Province of China(TW), Foreign company or corporation

CORE TERMS: acid, sodium, salt, derivative, statin, g-polyglutamic, ethanol, amine, calcium, formula, plusnn, carboxylic, dissolved, compound, substituting, simvastatin, mixture, ester, room temperature, carrier, preparation, alkyl, composition, pharmaceutical, alcohol, pharmaceutically, pulmonary, hydroxide, donated, ring

... 20090318459, December 24, 2009, United States of America (US) 8268847, September 18, 2012, United States of America (US)

13. 20110136818 (Note: This is a Patent Application only.), June 9, 2011, THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN, Clozel, Martine, Binningen, Swiss Confederation(CH), Swiss Confederation(); 058639, CLOZEL MARTINE, February 21, 2013, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:029850/0458

CORE TERMS: compound, receptor, macitentan, salt, prostacyclin, agonist, pulmonary, pharmaceutically, rat, hypertension, therapeutic, monocrotaline, administered, ingredient, endothelin, arterial, disease, route, cell, hypertensive, experimental, isopropyl, formula, variant, butoxy, amino, dose, invention relates, arterial blood, analogues

... GB], et al, United States of America (US) 8268847, September 18, 2012, CLOZEL MARTINE [CH ...

14. 20100311774 (Note: This is a Patent Application only.), December 9, 2010, Combination Comprising Paclitaxel for Treating Ovarian Cancer, Clozel, Martine, Binningen, Swiss Confederation(CH), Swiss Confederation(); Regenass, Urs, Allschwil, Swiss Confederation(CH), Swiss Confederation(); 867939, October 5, 2010, ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS)., ACTELION PHARMACEUTICALS LTD., GEWERBESTRASSE 16 CH 4123, ALLSCHWIL, SWITZERLAND( ), CH-4123, reel-frame:025089/0838, CLOZEL MARTINE; REGENASS URS

CORE TERMS: paclitaxel, compound, mice, formula, tumor, salt, cancer, pharmaceutically, ovarian, ascite, plusmn, formation, ensp, incidence, route, therapeutic, antagonist, ingredient, patient, i.p, pharmaceutical, experimental, endothelin, inhibition, suspension, receptor, assay, dose, administered, composition

... GB], et al, United States of America (US) 8268847, September 18, 2012, CLOZEL MARTINE [CH ...

US Patent Issued to Actelion Pharmaceuticals on Sept. 18 for "Therapeutic Compositions Comprising a Specific Endothelin Receptor Antagonist and a PDE5 Inhibitor" (Swiss Inventor)

US Fed News

September 23, 2012 Sunday 12:56 PM EST

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Length: 201 words

Dateline: ALEXANDRIA, Va.

Body

ALEXANDRIA, Va., Sept. 23 -- United States Patent no. 8,268,847, issued on Sept. 18, was assigned to Actelion Pharmaceuticals Ltd. (Allschwil, Switzerland).

"Therapeutic Compositions Comprising a Specific Endothelin Receptor Antagonist and a PDE5 Inhibitor" was invented by Martine Clozel (Binningen, Switzerland). According to the abstract released by the U.S. Patent & Trademark Office: "The invention relates to a product containing the compound of formula (I) belowor a pharmaceutically acceptable salt of this compound, in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved." The patent was filed on Aug. 28, 2007, under Application No. 12/439,290. For further information please visit: http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=8268847&OS=8268847&RS=8268847 For any query with respect to this article or any other content requirement, please contact Editor at itsyndication@hindustantimes.com

Classification

Language: ENGLISH

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Organization: PATENT & TRADEMARK OFFICE (57%)

Ticker: ATLN (SWX) (95%); ACT (FRA) (95%)

Industry: HORMONES, SUBSTITUTES & ANTAGONISTS (78%); BIOLOGICAL FACTORS (77%)

Geographic: VIRGINIA, USA (79%); UNITED STATES (73%)

Load-Date: September 23, 2012

Citing References (15)

Treatment	Title	Date	Type	Depth	Headnote(s)
Examined by	**1. EX PARTE MARTINE CLOZEL** 2016 WL 5787594, *1+ , Patent Tr. & App. Bd. This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1-14 of U.S. Patent Application No. 13/604,148 (''the '148 application''). We have jurisdiction under 35 U.S.C....	Sep. 29, 2016	Administrative Decision		—
Discussed by	**2. Appeal Brief Under 37 C.F.R. s 41.37** Out Of Plan Ex Parte Martine Clozel. 2013 WL 12123481, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	Dec. 27, 2013	Administrative Filing		—
Cited by	**3. Reply Brief Under 37 C.F.R. s 41.37** Out Of Plan Ex Parte Martine Clozel. 2014 WL 12576231, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	Aug. 26, 2014	Administrative Filing		—
Cited by	**4. Examiner's Answer** Out Of Plan Ex Parte Martine Clozel. 2014 WL 12576230, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	June 26, 2014	Administrative Filing		—
—	**5. PRODUCT, USEFUL TO TREAT E.G. HYPERTENSION AND HEART FAILURE, COMPRISES BROMO-PHENYL-BROMO-PYRIMIDINYLOXY-ETHOXY-PYRIMIDIN-YLAMINO-METHYL-PROPYL-AMINO SULFONYL AND COMPOUND HAVING PHOSPHODIESTERASE-5 INHIBITORY PROPERTIES** Out Of Plan DWPI 2008-J70674+	Aug. 29, 2006	DWPI	—	—
—	**6. COMBINATION COMPRISING MACITENTAN AND PACLITAXEL FOR TREATING MULTI-DRUG RESISTANT OVARIAN CANCER** Out Of Plan US PAT 8541433 , U.S. PTO Utility The invention relates to the combination of an endothelin receptor antagonist of formula (I) with paclitaxel, and in particular to this combination for therapeutic use,...	Sep. 24, 2013	Patents	—	—

Treatment	Title	Date	Type	Depth	Headnote(s)
—	**7. PROCESSES FOR PREPARING AMINE SALTS OF SILDENAFIL-ANALOGUES AND USE THEREOF** Out Of Plan US PAT 8497370 , U.S. PTO Utility A series of amine salts including a structure of formula (I) and formula (III) have provided. In formula I or formula (III), R 1, Ra and RX are as defined in the specification. The...	July 30, 2013	Patents	—	—
—	**8. RF 028787/0964** Out Of Plan	Aug. 15, 2012	Assignments	—	—
—	**9. THERAPEUTIC COMPOSITIONS** Out Of Plan US PAT APP 20130210830 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	Aug. 15, 2013	Patents	—	—
—	**10. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 9597331 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination with at least one compound...	Mar. 21, 2017	Patents	—	—
—	**11. STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING A PYRIMIDINE-SULFAMIDE** Out Of Plan US PAT 9265762 , U.S. PTO Utility The invention relates to stable pharmaceutical compositions comprising the compound of the below formula, or pharmaceutically acceptable salts, solvates, hydrates or morphological...	Feb. 23, 2016	Patents	—	—
—	**12. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 9173881 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination of at least one compound...	Nov. 03, 2015	Patents	—	—
—	**13. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 8809334 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination with at least one compound...	Aug. 19, 2014	Patents	—	—

Treatment	Title	Date	Type	Depth	Headnote(s)
—	**14. THERAPEUTIC COMPOSITIONS** Out of Res. US PAT APP 20140148460 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	May 29, 2014	Patents	—	—
—	**15. THERAPEUTIC COMPOSITIONS** Out of Res. US PAT APP 20130005734 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	Jan. 03, 2013	Patents	—	—

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Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 12439290 **Filing Dt:** 02/27/2009 **Patent #:** 8268847 **Issue Dt:** 09/18/2012
PCT #: NONE **Intl Reg #:** **Publication #:** US20090318459 **Pub Dt:** 12/24/2009
Inventor: Martine Clozel
Title: THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

Assignment: 1

Reel/Frame: 028787 / 0964 **Received:** 08/15/2012 **Recorded:** 08/15/2012 **Mailed:** 08/16/2012 **Pages:** 3
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).
Assignor: CLOZEL, MARTINE **Exec Dt:** 01/20/2009
Assignee: ACTELION PHARMACEUTICALS LTD.
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Web interface last modified: Aug 20, 2015 v.2.5

UNITED THERAPEUTICS CORP., EX1003, page 258
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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Patent Owner's Name and Address:

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OC000000094320044

Patent Number: 8268847 Control Number: 96/000,237 Date Mailed: 09/26/2017

NOTICE OF SUPPLEMENTAL EXAMINATION REQUEST FILING DATE

The patent owner is hereby notified that the filing date of the request for supplemental examination is 09/22/2017, the date that a request meeting all of the applicable requirements of 37 CFR §§ 1.605, 1.610, and 1.615 was received by the Office.

A supplemental examination certificate will issue within three months from the filing date of the request for supplemental examination. See 37 CFR 1.625.

This notice is being sent to the official correspondence address of record which, in a supplemental examination proceeding, is the official correspondence address of record in the patent file. See 37 CFR 1.33.

/RBELL/

Central Reexamination Unit
(571) 272-1549, FAX NO. (571)273-9900

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,237	09/22/2017	8268847		5019

45511 7590 10/25/2017

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EXAMINER
KUGEL, TIMOTHY J

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
10/25/2017	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

(12) SUPPLEMENTAL EXAMINATION CERTIFICATE

United States Patent (10) **Number: US 8,268,847 F1**

Clozel (45) **Certificate Issued: Oct. 25, 2017**

Control No.: 96/000,237 **Filing Date: Sep. 22, 2017**

Primary Examiner: Timothy J. Kugel

A substantial new question of patentability affecting at least one claim of the patent is raised in the request for supplemental examination. See the Reasons for Substantial New Question of Patentability Determination in the file of this proceeding. Accordingly, ex parte reexamination will be ordered pursuant to 35 U.S.C. 257.

(56) **Items of Information**

U.S. PATENT DOCUMENTS

US 7,094,781 F1	08/2006	Bolli et al.
US 8,367,685 F1	02/2013	Adesuyi et al.

FOREIGN PATENT DOCUMENTS

WO	02/053557 A1	07/2002
WO	2006/026395 A1	03/2006

OTHER DOCUMENTS

Office Action mailed February 28, 2012 during prosecution of the '847 patent

UNITED THERAPEUTICS CORP., EX1003, page 261
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,237	09/22/2017	8268847		5019

45511 7590 10/25/2017

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EXAMINER
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10/25/2017	PAPER

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REASONS FOR SUBSTANTIAL NEW QUESTION OF PATENTABILITY DETERMINATION

Review of Pertinent File History

A supplemental examination request was filed 22 September 2017 and assigned control number 96/000237 (the '237 Request).

On 26 September 2017, the Office mailed a "Notice of Supplemental Examination Request Filing Date" indicating the '237 Request was granted a filing date. See MPEP §2812.01.

The '237 Request requests supplemental examination of all the claims (**claims 1-11**) of US Patent 8,268,847 (the '847 patent) which issued to Clozel, on 18 September 2012.

Items of Information

The '237 Request requests supplemental examination in view of the following five (5) items of information:

1. US Patent 7,094,781 issued to Bolli *et al.* on 22 August 2006, hereinafter BOLLI '781[1].
2. US Patent 8,367,685 issued to Adesuyi *et al.* on 05 February 2013, hereinafter ADESUYI[2].
3. International Application Publication WO 02/053557 by Bolli *et al.*, published on 11 July 2002, hereinafter BOLLI '557[1].
4. International Application Publication WO 2006/026395 by Keyser *et al.*, published on 09 March 2006, hereinafter KEYSER[1].

[1] BOLLI '781, BOLLI '557, and KEYSER each qualifies as prior art under 35 USC §102(b).
[2] ADESUYI does not qualify as prior art under 35 USC §102, but raises the issue of non-statutory double patenting.

5. Final rejection in Application 12/439290 mailed on 28 February 2012, hereinafter OFFICE ACTION.

The '847 Patent

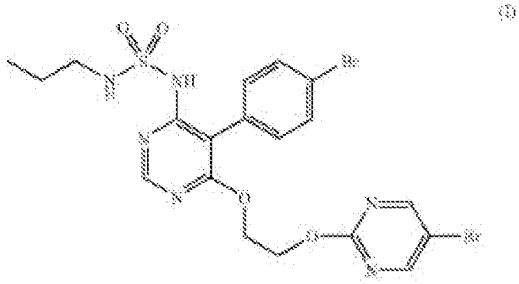
The '847 patent was filed as US patent application 12/439,290 (the '290 application) on 27 February 2009. The '290 application is a national stage entry under 35 USC §371 of PCT/IB07/53448 filed on 28 August 2007, and claims foreign priority to PCT/IB2006/052999 filed on 29 August 2006, and PCT/IB2006/053857 filed on 19 October 2006.

During prosecution of the '290 application, the examiner stated in the reasons for allowance (Notice of Allowance mailed 21 May 2012, p.4):

> The claims 1-12 are drawn to a composition comprising a compound of formula (I) and a compound having PDE5-inhibitor activity for the treatment of hypertension or pulmonary hypertension. The prior art does not teach the compound of formula (I) in combination with a compound that has PDE5-ihibitor properties. The closest art is applicant's own work (Bolli et al. of record), which teaches that the compound of formula (I) has ET antagonist activity and can be used to treat conditions or diseases which are associated with an increase in vasoconstriction such as hypertension. Since the Applicant's have established that Bolli et al. is Applicant's own work, the reference cannot be used as a reference under U.S.C. 103(c) for the 103(a) rejection.

Of the 11 issued claims, **claim 1** is independent. **Claim 1** is reproduced below:

> 1. A product containing the compound of formula (I) below



in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

Analysis

The Following Items of Information Raise a Substantial New Question of Patentability:

BOLLI '781:

Item 1. BOLLI '781, as presented in the '237 Request, raises a substantial new question of patentability affecting **claims 1-11** of the '847 patent because BOLLI '781 teaches limitations determined to be missing from the prior art of record cited during the prosecution of the '290 application that led to the issuance of the '847 patent. See MPEP §2816.03 II.

In particular, BOLLI '781 teaches the compound of formula (I) as claimed (Chemical Structure at 22:1-14), used for treatment of diseases which are associated with an increase in vasoconstriction; specifically exemplifying hypertension, pulmonary hypertension, heart failure and erectile dysfunction (1:44-55 and 5:25-46). BOLLI '781 further teaches that preparations with the compound in combination with pharmacodynamically active excipients (5:55-64).

During the prosecution of the '290 application, the examiner considered BOLLI '781, but only in combination with BOLLI '557, which was erroneously believed to be disqualified, under 35 USC §103(c), for use in rejections under 35 USC §103(a).

In light of the prosecution history of the '290 application, a reasonable examiner would consider the teachings of BOLLI '781 important in deciding whether **claims 1-11** of the '847 patent are patentable.

ADESUYI:

Item 2. ADESUYI, as presented in the '237 Request, raises a substantial new question of patentability affecting **claims 1-11** of the '847 patent because ADESUYI claims limitations determined to be missing from the prior art of record cited during the prosecution of the '290 application that led to the issuance of the '847 patent. See MPEP §2816.03 II.

In particular, ADESUYI claims the treatment of pulmonary arterial hypertension comprising the administration to a patient in need thereof a pharmaceutical composition comprising the compound of formula (I) (Claims 1, 8 and 16).

During the prosecution of the '290 application, the examiner considered the application that matured into ADESUYI (US Application 12/388142), but only in combination with BOLLI '557, which was erroneously believed to be disqualified, under 35 USC §103(c), for use in rejections under 35 USC §103(a).

In light of the prosecution history of the '290 application, a reasonable examiner would consider the claims of ADESUYI important in deciding whether **claims 1-11** of the '847 patent are patentable.

BOLLI '557:

Item 3. BOLLI '557, as presented in the '237 Request, raises a substantial new question of patentability affecting **claims 1-11** of the '847 patent because BOLLI '557 teaches limitations determined to be missing from the prior art of record cited during the

prosecution of the ‘290 application that led to the issuance of the ‘847 patent. See MPEP §2816.03 II.

In particular, BOLLI ‘557 teaches claimed compound formula (I) (p.28, Row 1 Column 1) as an active ingredient, endothelin receptor antagonist, in the preparation of pharmaceutical compositions in compositions (Abstract). BOLLI ‘557 further teaches that the compound formula (I) can be combined with an excipient and another active compound to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (p.16 ¶1 and p.17 ¶3).

During the prosecution of the ‘290 application, the examiner considered BOLLI '557, in combination with BOLLI ‘178, the application that matured into ADESUYI, and KEYSER; but BOLLI ‘557 was erroneously believed to be disqualified, under 35 USC §103(c) , for use in rejections under 35 USC §103(a).

In light of the prosecution history of the ‘290 application, a reasonable examiner would consider the teachings of BOLLI ‘557 important in deciding whether **claims 1-11** of the ‘847 patent are patentable.

KEYSER:

Item 4. KEYSER, as presented in the ‘237 Request, raises a substantial new question of patentability affecting **claims 1-11** of the ‘847 patent because KEYSER teaches limitations determined to be missing from the prior art of record cited during the prosecution of the ‘290 application that led to the issuance of the ‘847 patent. See MPEP §2816.03 II.

In particular, KEYSER teaches the combination of an endothelin receptor antagonist and a PDE5 inhibitor are useful together to treat cardiac disorders such as pulmonary arterial hypertension (Abstract) and further teaches that the PDE5 inhibitor may be, *inter alia*, tadalafil (Claims 19 and 21).

During the prosecution of the '290 application, the examiner considered KEYSER, but only in combination with BOLLI '557, which was erroneously believed to be disqualified, under 35 USC §103(c), for use in rejections under 35 USC §103(a).

In light of the prosecution history of the '290 application, a reasonable examiner would consider the teachings of KEYSER important in deciding whether **claims 1-11** of the '847 patent are patentable.

The Following Items of Information Do Not Raise a Substantial New Question of Patentability:

The OFFICE ACTION:

Item 5. The OFFICE ACTION, as presented in the '237 Request, does not raise a substantial new question of patentability affecting **claims 1-11** of the '847 patent. See MPEP §2816.03 II.

The OFFICE ACTION summarizes the teachings of the above **Items 1-4**.

The OFFICE ACTION does not provide any teaching relative to those limitations determined to be missing from the prior art during prosecution of the '290 application.

In light of the prosecution history of the '290 application, a reasonable examiner would NOT consider the teachings of the OFFICE ACTION important in deciding whether **claims 1-11** of the '847 patent are patentable.

/Timothy J. Kugel/
Patent Reexamination Specialist
Central Reexamination Unit 3991

Conferees:

/Dwayne Jones/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/Jean Witz/
Supervisory Patent Reexamination Specialist
Central Reexamination Unit 3991

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,237	09/22/2017	8268847		5019

45511 7590 11/13/2017

Baker & Hostetler LLP
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PHILADELPHIA, PA 19104-2891

EXAMINER
KUGEL, TIMOTHY J

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
11/13/2017	PAPER

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Office Action in Ex Parte Reexamination	Control No. 96/000,237	Patent Under Reexamination 8268847	
	Examiner Timothy J. Kugel	Art Unit 3991	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a. ☐ Responsive to the communication(s) filed on _____ .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

b. ☐ This action is made FINAL.

c. ☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-11* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-11* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☒ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the certified copies have
   1 ☐ been received.
   2 ☐ not been received.
   3 ☒ been filed in Application No. *12/439,290* .
   4 ☐ been filed in reexamination Control No. _____.
   5 ☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

UNITED THERAPEUTICS CORP., EX1003, page 271
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Reexamination Ordered Pursuant to 35 USC §257

The supplemental examination proceeding, filed on 22 September 2017, concluded with the issuance of the supplemental examination certificate on 25 October 2017. The certificate indicated that one or more of the items of information submitted as part of the request for supplemental examination raises a substantial new question of patentability. See the Reasons for Substantial New Question of Patentability Determination in the file of this proceeding.

Accordingly, *ex parte* reexamination of **claims 1-11** of US Patent 8,268,847 is ordered. See 35 USC §257(b) and 37 CFR §1.625(b).

This *ex parte* reexamination proceeding is hereby initiated by the mailing of this order. *Ex parte* reexamination under 35 USC §257 will be conducted in accordance with 37 CFR §§1.530 through 1.570, which govern *ex parte* reexamination, subject to the exceptions enumerated in 37 CFR §1.625(d), and, in addition, to the exception that a patent owner's statement, including any amendment, under 37 CFR §1.530(a)-(c) may not be filed. See 35 USC §257(b). For this reason, no amendment in an *ex parte* reexamination proceeding ordered under 35 USC §257 may be filed until after the mailing of a first Office action on the merits (which appears below).

This reexamination proceeding has been assigned to the art unit listed at the top of the cover page of this action. All future correspondence should be directed to the assigned

art unit and should be identified by the control number, which is also listed at the top of the cover page of this action, and which is identical to the control number assigned to the now-concluded supplemental examination proceeding. A first Office action on the merits appears below.

Since the patent under reexamination has an effective filing date prior to 16 March 2013, this reexamination proceeding is taking place under the pre-AIA first to invent provisions.

In accordance with MPEP §2256, the examiner has reviewed and considered the prior art cited in the Parent Application; therefore, all documents cited or considered 'of record' in the Parent Application are now considered cited or 'of record' in this reexamination.

Patent owner is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR §§1.121(j) and 1.530(d)-(j). See MPEP §2234.

First Office Action on the Merits
Status of the Proceeding

On 22 September 2017	A Request for Supplemental Examination of **claims 1-11** of US Patent 8,268,847 (the '847 patent) was filed by Patent Owner.
On 26 September 2017	A Notice of Supplemental Examination Request Filing Date was mailed.
On 25 October 2017:	A Supplemental Examination Certificate, noting that a substantial new question of patentability affecting at least

one claim of the '847 patent was raised in the request for supplemental examination, was mailed.

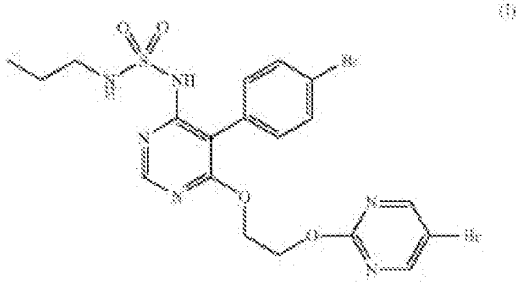
Priority

The '847 patent was filed as US Patent application 12/439290 (the '290 application) on 27 February 2009. The '290 application was a national stage entry under 35 USC §371 of PCT/IB07/53448 filed on 28 August 2007, and claimed foreign priority to PCT/IB2006/052999 filed on 29 August 2006, and PCT/IB2006/053857 filed on 19 October 2006.

Claim Scope and Interpretation

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F2nd 1569, 1571 222 USPQ 934,936 (Fed Cir 1984) claims are given "their broadest reasonable interpretation consistent with the specification".

The '847 patent contains **claims 1-11** directed to a product of FORMULA (I) and at least one compound having PDE5 inhibitory properties. Independent **claim 1** is representative:

> 1. A product containing the compound of Formula (I) below
>
> 
>
> in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable

salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

References Cited

The following references are cited in this Office action:

- US Patent 7,094,781 issued to Bolli *et al.* on 22 August 2006, hereinafter BOLLI '781[1].
- US Patent 8,367,685 issued to Adesuyi *et al.* on 05 February 2013, hereinafter ADESUYI[2].
- International Application Publication WO 02/053557 by Bolli *et al.*, published on 11 July 2002, hereinafter BOLLI '557[1].
- International Application Publication WO 2006/026395 by Keyser *et al.*, published on 09 March 2006, hereinafter KEYSER[1].

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F3d 1428, 46 USPQ2d 1226 (Fed Cir 1998); *In re Goodman*, 11 F3d 1046, 29 USPQ2d 2010 (Fed Cir 1993); *In re Longi*, 759 F2d 887, 225 USPQ 645 (Fed Cir 1985); *In re Van Ornum*, 686 F2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR §§1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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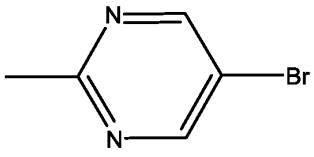
[1] BOLLI '781, BOLLI '557, and KEYSER each qualifies as prior art under pre-AIA 35 USC §102(b).
[2] ADESUYI does not qualify as prior art under pre-AIA 35 USC §102, but raises the issue of non-statutory double patenting.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR §3.73(b).

1. **Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 9 of BOLLI '781 in view of KEYSER**.

BOLLI '781 and the patent under reissue are both assigned to Actelion Pharmaceuticals, Ltd. and have overlapping inventive entities.

Although the conflicting claims are not identical in that BOLLI '781 does not claim the compound of FORMULA (I) in combination with a compound having PFE5-inhibitory properties, they are not patentably distinct from each other because of the following:

Regarding **claim 1**, BOLLI '781 claims a compound, designated FORMULA V, or a pharmaceutically acceptable salt thereof (Claims 8 and 9). FORMULA V of BOLLI '781 meets claimed FORMULA (I) when R^1 is a lower alkyl, specifically $CH_3(CH_2)_2$, and R^5 is a heteroaryl, specifically a bromopyrimidine 

. The claimed compound of FORMULA (I) is exemplified by BOLLI '781 (Column 22, first compound) and is described as an endothelin receptor (ET) antagonist (Abstract). See *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

BOLLI '781 does not claim the compound of FORMULA (I) being in combination with a PDE-5 inhibitor as claimed.

KEYSER claims methods of treating pulmonary hypertension comprising administering a PDE5 inhibitor and an endothelin receptor (ET) antagonist (Claim 1).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to include the PDE5 inhibitor of KEYSER in a composition containing the compound of FORMULA (I) as claimed by BOLLI '781. The rationale for doing so would have been the teaching of KEYSER that such combination is effective in treating pulmonary hypertension (Abstract and Claim 1).

Regarding **claims 2-4, 7-9 and 11**, KEYSER claims the PDE5-inhibitor as being, *inter alia*, vardenafil, tadalafil or sildenafil (Claim 9).

Regarding **claims 5 and 10**, KEYSER claims such compositions for use in treating vascular conditions such as hypertension (Claim 15).

Regarding **claim 6**, BOLLI '781 discloses that the compound can be made into preparations comprising excipients (5:55-65). See *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

2. **Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of ADESUYI, as evidenced by BOLLI '557, in view of KEYSER**.

ADESUYI and the patent under reissue are both assigned to Actelion Pharmaceuticals, Ltd.

Although the conflicting claims are not identical in that ADESUYI does not claim the compound of FORMULA (I) in combination with a compound having PFE5-inhibitory properties, they are not patentably distinct from each other because of the following:

Regarding **claim 1**, ADESUYI claims a compound of FORMULA (I) or a pharmaceutically acceptable salt, solvate, hydrate or morphological form thereof (Claims 1 and 8). ADESUYI further claims such composition for use in treating pulmonary arterial hypertension (Claims 15 and 16), a disease involving vasoconstriction.

BOLLI ‘557 shows that the claimed compound of ADESUYI, FORMULA (I), (BOLLI ‘557 p.28, Row 1 Column 1) is an endothelin receptor (ET) antagonist, and can be used as an active ingredient in the preparation of pharmaceutical compositions (Abstract). BOLLI ‘557 further shows that the claimed compound of ADESUYI, FORMULA (I), can be combined with an excipient and other active compound(s) to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (p.16 ¶1 and p.17 ¶3).

ADESUYI does not claim the compound of FORMULA (I) in combination with a PDE-5 inhibitor as claimed.

KEYSER claims methods of treating pulmonary hypertension comprising administering a PDE5 inhibitor and an ET antagonist (Claim 1).

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to include the PDE5 inhibitor of KEYSER in the composition containing the compound of FORMULA (I) of ADESUYI, given that BOLLI '557 provides evidence

that the compound of FORMULA (I) of ADESUYI and the instant claims is an ET antagonist. The rationale for doing so would have been the teaching of KEYSER that such combination is effective in treating pulmonary hypertension (Abstract and Claim 1).

Regarding **claims 2-4, 7-9 and 11**, KEYSER claims the PDE5-inhibitor as being, *inter alia*, vardenafil, tadalafil or sildenafil (Claim 9).

Regarding **claims 5 and 10**, ADESUYI, as above, claims such compositions for use in treating pulmonary arterial hypertension (Claims 15 and 16).

Regarding **claim 6**, ADESUYI claims the composition further comprises a filler, disintegrate, surfactant and lubricant (Claims 1 and 8), which ADESUYI describes as excipients (2:62-3:07).

Claim Rejections - 35 USC §103

The following is a quotation of pre-AIA 35 USC §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. **Claims 1-11 are rejected as being unpatentable under pre-AIA 35 USC §103(a) as being obvious over KEYSER in view of BOLLI '781**.

KEYSER claims methods of treating pulmonary hypertension comprising administering a PDE5 inhibitor and an ET antagonist (Claim 1).

KEYSER does not expressly disclose the compound of FORMULA (I) as being the specific ET antagonist.

Regarding **claim 1**, BOLLI '781 teaches the compound of FORMULA (I) as claimed (Chemical Structure at 22:1-14), used for treatment of diseases which are associated with an increase in vasoconstriction; specifically exemplifying hypertension, pulmonary hypertension, heart failure and erectile dysfunction (1:44-55 and 5:25-46). BOLLI '781 further identifies such compound as an endothelin receptor antagonist (Abstract and 8:25-31 *inter alia*).

At the time of the invention it would have been obvious to a person of ordinary skill in the art to replace the ET antagonist of KEYSER with the compound of FORMULA (I) of BOLLI '781 since BOLLI '781 teaches that they are functionally equivalent and are used for the same intended purpose. See MPEP §2144.06(II) and *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958); and MPEP §2144.07 and *Sinclair & Carroll Co v Interchemical Corp*, 325 US 327, 65 USPQ 297 (1945).

Regarding **claims 2-4, 7-9 and 11**, KEYSER claims the PDE5-inhibitor as being, *inter alia*, vardenafil, tadalafil or sildenafil (Claim 9).

Regarding **claims 5 and 10**, as above, BOLLI '781 teaches the compound of FORMULA (I) as claimed (Chemical Structure at 22:1-14), used for treatment of diseases which are associated with an increase in vasoconstriction; specifically exemplifying hypertension, pulmonary hypertension, heart failure and erectile dysfunction (1:44-55 and 5:25-46). Further, KEYSER claims such combined compositions for use in treating vascular conditions such as hypertension (Claim 15).

Regarding **claim 6**, BOLLI '781 discloses that the compound can be made into preparations comprising excipients (5:55-65).

4. **Claims 1-11 are rejected as being unpatentable under 35 USC §103(a) as being obvious over KEYSER in view of BOLLI '557**.

KEYSER claims methods of treating pulmonary hypertension comprising administering a PDE5 inhibitor and an ET antagonist (Claim 1).

KEYSER does expressly disclose the compound of FORMULA (I) being the specific ET antagonist as claimed.

Regarding **claim 1**, BOLLI '557 discloses claimed compound FORMULA (I) (p.28, Row 1 Column 1) and teaches that it is an endothelin receptor (ET) antagonist, and can be used as an active ingredient in the preparation of pharmaceutical compositions (Abstract). BOLLI '557 further discloses that the compound FORMULA (I) can be combined with an excipient and other active compound(s) to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (p.16 ¶1 and p.17 ¶3).

At the time of the invention it would have been obvious to a person of ordinary skill in the art to replace the ET antagonist of KEYSER with the compound of FORMULA (I) of BOLLI '557 since BOLLI '557 teaches that they are functionally equivalent and are used for the same intended purpose. See MPEP §2144.06(II) and *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958); and MPEP §2144.07 and *Sinclair & Carroll Co v Interchemical Corp*, 325 US 327, 65 USPQ 297 (1945).

Regarding **claims 2-4, 7-9 and 11**, KEYSER claims the PDE5-inhibitor as being, *inter alia*, vardenafil, tadalafil or sildenafil (Claim 9).

Regarding **claims 5 and 10**, as detailed above, BOLLI '557 teaches that the compound FORMULA (I) can be used to treat conditions or disease which are associated with an increase in vasoconstriction such as hypertension and erectile dysfunction (p.16 ¶1 and p.17 ¶3). Further, KEYSER claims such combined compositions for use in treating vascular conditions such as hypertension (Claim 15).

Regarding **claim 6**, as above, BOLLI '557 further discloses that the compound FORMULA (I) can be combined with an excipient and other active compound(s) (p.16 ¶1 and p.17 ¶3). Further, ADESUYI claims the composition further comprises a filler, disintegrate, surfactant and lubricant (Claims 1 and 8), which ADESUYI describes as excipients (2:62-3:07).

Conclusion

Status of the claims:

Claims 1-11 are subject to reexamination.

Claims 1-11 are rejected

Duty of Disclosure

The patent owner is reminded of the continuing responsibility under 37 CFR §1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving US Patent 8,268,847 throughout the course of this reexamination proceeding. See MPEP §§2207, 2282 and 2286.

Response

A shortened statutory period of response to this action is set to expire two (2) months from the mailing of this Office action. Failure to respond within this period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. See 37 CFR §1.550.

EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR §1.550(c).

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR §1.116, after final rejection and 37 CFR §41.33 after appeal, which will be strictly enforced.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy J. Kugel whose telephone number is (571) 272-1460. The examiner works a flexible schedule, but can normally be reached on Monday - Thursday 0700 to 1730 Eastern Time.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jean Witz, can be reached on (571) 272-0927.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Telephone Numbers for reexamination inquiries:

Central Reexamination Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission	(571) 273-9900

Please mail any communications to:

Mail Stop *Ex Parte* Reexam
ATTN: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By EFS:

Registered users may submit via the electronic filing system EFS-Web at:

https://efs.uspto.gov/efile/myportal/efs-registered

For EFS-Web transmission, 37 CFR §1.8(a)(1)(i)(C) and (ii) states that correspondence (except for a request for reexamination and a corrected or replacement request for reexamination) will be considered timely filed if (a) it is transmitted via the Office's electronic filing system in accordance with 37 CFR §1.6(a)(4), and (b) includes a certificate of transmission for each piece of correspondence stating the date of transmission, which is prior to the expiration of the set period of time in the Office Action.

Please FAX to:
(571) 273-9900
Central Reexamination Unit

Please Hand Deliver to:
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

/Timothy J. Kugel/
Patent Reexamination Specialist, CRU 3991

Conferees:

/Dwayne Jones/
Patent Reexamination Specialist, CRU 3991

/Jean C. Witz/
Supervisory Patent Reexamination Specialist, CRU 3991

Notice of References Cited	Application/Control No. 96/000,237	Applicant(s)/Patent Under Reexamination 8268847	
	Examiner Timothy J. Kugel	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-7,094,781 B2	08-2006	Bolli; Martin	C07D239/47	514/235.8
*	B	US-8,367,685 B2	02-2013	Adesuyi; Charles Tokunbo	A61K9/1652	514/275
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
*	N	WO 02053557 A1	07-2002	SWITZERLAND	WELLER THOMAS	C07D239/47
*	O	WO 2006026395 A1	03-2006	UNITED STATES	DIXON RICHARD	A61K31/505
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Office Action mailed February 28, 2012 during prosecution of US Patent 8,268,847
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 5019

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
96/000,237	09/22/2017 RULE	514	3991	

APPLICANTS

INVENTORS

8268847, Residence Not Provided;
ACTELION PHARMACEUTICALS, LTD., ALLSCHWIL, SWITZERLAND;
PATENT OWNER, Residence Not Provided;

**** CONTINUING DATA ***********************

This application is a SER of 12/439,290 02/27/2009 PAT 8268847
which is a 371 of PCT/IB07/53448 08/28/2007

**** FOREIGN APPLICATIONS ***********************

INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/052999 08/29/2006
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/053857 10/19/2006

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /TIMOTHY J KUGEL/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS

ADDRESS

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891
UNITED STATES

TITLE

THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

FILING FEE RECEIVED		
0.00	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,237	09/22/2017	8268847		5019

45511 7590 12/27/2017

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER
KUGEL, TIMOTHY J

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
12/27/2017	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)		
	96/000,237	8268847		
	Examiner	Art Unit	AIA (First Inventor to File) Status	Page
	Timothy J. Kugel	3991	No	1 of 2

All participants (applicant, applicant's representative, PTO personnel):

1. Timothy J. Kugel (Primary Examiner); WebEx/Video Conference
2. Kendra Carter (Primary Examiner); WebEx/Video Conference
3. Dwayne Jones (Primary Examiner); WebEx/Video Conference
4. Jean Witz (SPE); In-Person
5. David Farsiou (Attorney of Record); In-Person
6. Joseph Lucci (Attorney of Record); In-Person

Date of Interview: 20 December 2017

Claim(s) discussed: Claims in general.

Identification of prior art discussed: WO2006/026395 (KEYSER), US 7,094,781 (BOLLI '781), WO02/053557 (BOLLI '557)

Brief Description of main topic of discussion: Applicant is considering making the same argument that the Patents Trial and Appeal Board (PTAB) found convincing in Application 13/604148, which had rejections under 35 USC 103(a) over the same combination of references as the instant reexamination.

It was agreed that the panel would review the PTAB decision, made of record in this reexamination as Exhibit E of the Request for Supplemental Examination filed on 22 September 2017. After this review, applicant and Examiner Kugel will conduct another interview to discuss any issues making such an argument in this case might raise.

Issues Discussed:

/Timothy J. Kugel/ Patent Reexamination Specialist, CRU 3991	/Jean Witz/ Supervisory Patent Reexamination Specialist, CRU 3991

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable time limit of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Applicant-Initiated Interview Summary	Application No.	Applicant(s)		
	96/000,237	8268847		
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4. Jean Witz (SPE); In-Person
5. David Farsiou (Attorney of Record); In-Person
6. Joseph Lucci (Attorney of Record); In-Person

Date of Interview: 20 December 2017

Claim(s) discussed: Claims in general.

Identification of prior art discussed: WO2006/026395 (KEYSER), US 7,094,781 (BOLLI '781), WO02/053557 (BOLLI '557)

Brief Description of main topic of discussion: Applicant is considering making the same argument that the Patents Trial and Appeal Board (PTAB) found convincing in Application 13/604148, which had rejections under 35 USC 103(a) over the same combination of references as the instant reexamination.

It was agreed that the panel would review the PTAB decision, made of record in this reexamination as Exhibit E of the Request for Supplemental Examination filed on 22 September 2017. After this review, applicant and Examiner Kugel will conduct another interview to discuss any issues making such an argument in this case might raise.

Issues Discussed:

/Timothy J. Kugel/ Patent Reexamination Specialist, CRU 3991	/Jean Witz/ Supervisory Patent Reexamination Specialist, CRU 3991

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable time limit of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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Fax Cover Sheet

Date: January 16, 2018 **Pages (including cover sheet):** 28

Name	Company	Fax #	Phone #
Examiner Timothy J. Kugel and Reexamination	United States Patent and Trademark Office	571-273-8300 and 571-273-9900	

From: David N. Farsiou
Client Matter #: 103693.000585
Re: In re Reexamination of Martine CLOZEL
Control No. 96/000,237
Filing Date: September 22, 2017
Confirmation No. 5019
Group Art Unit 3391
Examiner: Timothy J. Kugel

Message:

Attached hereto are the following documents for filing via facsimile:

Amendment In Ex Parte Reexamination Pursuant to 37 CFR 1.550 and 37 CFR 1.111 with facsimile certification (12 pages)

Exhibit A - Ex parte Clozel, Appeal 2014-009320 (Oct. 3, 2016) ("Decision") (14 pages)

Fee Transmittal (1) Refaxing Fee Transmittal 1 page
ONE page

If this transmission is not complete, please call David N. Farsiou at 215.564.8984.

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PAGE 1/2 * RCVD AT 1/16/2018 6:55:46 PM [Eastern Standard Time] * SVR:W-PTOFAX-002/36 * DNIS:2738300 * CSID: * DURATION (mm-ss):00-52

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FEE TRANSMITTAL

Complete if known	
Application Number	96/000,237
Filing Date	September 22, 2017
First Named Inventor	Martine CLOZEL
Examiner Name	Timothy J. Kugel
Art Unit	3991
Practitioner Docket No.	103693.000585

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 3,700.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 233050 23-3050 Deposit Account Name: Dilworth & Hostetler LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, except for the filing fee

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	300	150*	75	660	330	165	760	380	190	
Design	200	100	50	160	80	40	600	300	150	
Plant	200	100	50	420	210	105	620	310	155	
Reissue	300	150	75	660	330	165	2,200	1,100	550	
Provisional	280	140	70	0	0	0	0	0	0	

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	100	50	25
Each independent claim over 3 (including Reissues)	460	230	115
Multiple dependent claims	820	410	205

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
57	-20 or HP =	37	x	100	=	3,700.00

HP = highest number of total claims paid for, if greater than 20.

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
	-3 or HP =	0	x	0	=	0

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number)	x	_____	=	_____

4. OTHER FEE(S) Fees Paid ($)

Non-English specification, $130 fee (no small or micro entity discount) _____

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity) _____

Other (e.g., late filing surcharge): _____ _____

SUBMITTED BY

Signature	/David N. Farsiou/	Registration No. (Attorney/Agent) 44,104	Telephone 215-568-3100
Name (Print/Type)	David N. Farsiou		Date January 16, 2018

This collection of information is required by 37 CFR 1.196. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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DOCKET NO.: 103693.000585
Control No.: 96/000,237
Office Action Dated: November 13, 2017

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination of:

Martine CLOZEL

Control No.: 96/000,237

Filing Date: September 22, 2017

Patent No.: 8,268,847

Confirmation No.: 5019

Group Art Unit: 3991

Examiner: Timothy J. Kugel

Therapeutic Compositions Comprising A Specific Endothelin Receptor Antagonist And A PDE5 Inhibitor

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Dear Commissioner

Certificate of Facsimile Transmission
Date: January 16, 2018
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office to facsimile number 571-273-8300
/ David N. Farsiou /
David N. Farsiou, Reg. No. 44,104

AMENDMENT IN EX PARTE REEXAMINATION PURSUANT TO 37 CFR § 1.550 AND 37 C.F.R. § 1.111

In response to the Official Action dated November 13, 2017, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

☐ **Amendments to the Specification** begin on page of this paper.

☐ **Amendments to the Abstract** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.

☒ **Remarks** begin on page 8 of this paper.

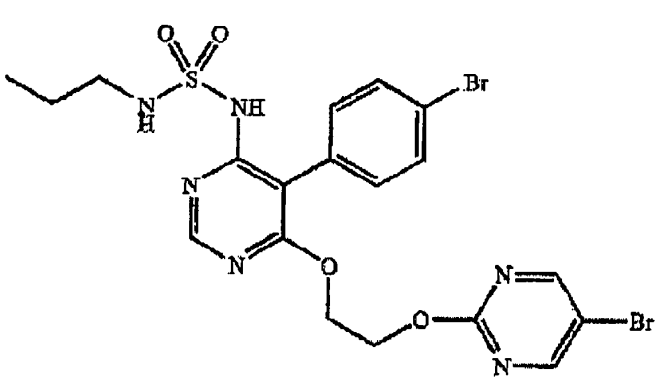
☒ The Commissioner is hereby authorized to charge any fee deficiency, charge any additional fees, or credit any overpayment of fees, associated with this application in connection with this filing, or any future filing, submitted to the U.S. Patent and Trademark Office during the pendency of this application, to Deposit Account No. 23-3050.

PAGE 2/28 * RCVD AT 1/16/2018 6:35:01 PM [Eastern Standard Time] * SVR:W-PTOFAX-002/3 * DNIS:2738300 * CSID: * DURATION (mm-ss):07-15

UNITED THERAPEUTICS CORP., EX1003, page 295
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Listing of Claims:

1. A product containing the compound of formula (I) below:



(I)

in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.

4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.

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U.S. PATENT 8,268,847

5. The product according to claim 1, wherein the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.

6. A pharmaceutical composition containing, as active principles, the compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form, as well as at least one excipient.

7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.

10. A method for the treatment of hypertension or pulmonary hypertension comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

12. (New) The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. (New) The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.

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U.S. PATENT 8,268,847

14. (New) The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. (New) The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. (New) The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. (New) The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

18. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.

21. (New) The method of claim 20, wherein the interval between the administration of the compound of formula (I) and the administration of tadalafil does not exceed two days.

22. (New) The method of claim 21, wherein the interval does not exceed one day.

23. (New) The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

24. (New) The method of claim 23, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

25. (New) The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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26. (New) The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

27. (New) The method of claim 26, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

28. (New) The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

29. (New) The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

30. (New) The method of claim 29, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

31. (New) The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

32. (New) The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

33. (New) The method of claim 32, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

34. (New) The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

35. (New) The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

36. (New) The method of claim 35, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

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37. (New) The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

38. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

41. (New) The method of claim 40, wherein the interval between the administration of the compound of formula (I) and the administration of sildenafil does not exceed two days.

42. (New) The method of claim 41, wherein the interval does not exceed one day.

43. (New) The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

44. (New) The method of claim 43, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

45. (New) The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

46. (New) The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

47. (New) The method of claim 46, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

48. (New) The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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49. (New) The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

50. (New) The method of claim 49, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

51. (New) The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

52. (New) The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

53. (New) The method of claim 52, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

54. (New) The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

55. (New) The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

56. (New) The method of claim 55, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

57. (New) The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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REMARKS

Following entry of the present amendments, claims 1-57 will be pending in this *ex parte* reexamination of U.S. Patent No. 8,268,847 ("the 847 Patent"). Claims 1-11 are original claims. New claims 12-57 are being added herein.

Support for the new claims may be found at, for example, the originally filed claims and col. 2, lines 36-39, col. 4, lines 25-28 (pulmonary arterial hypertension); col. 2, lines 15-35, col. 3, lines 36-57 (administration); and col. 4, lines 7-18 (dosage amounts) of the 847 Patent.

The new claims are patentable for at least the same reasons as the claims from which they depend.

Examiner Interview Summary

Patentee's undersigned counsel would like to thank the Central Reexamination Unit panel for the interview on December 20, 2017. The panel included examiners Timothy Kugel, Dwayne Jones, and Kendra Carter, and supervisory examiner Jean Witz. David Farsiou and the undersigned attended on behalf of Patentee. Patentee agrees with the summary reflected in the Applicant Initiated Interview Summary, dated December 27, 2017, namely that the panel agreed to review the Patent Trial and Appeal Board ("Board") decision rendered in Application No. 13/604,148 ("the '148 application") to determine whether making an argument consistent with the Board decision would address the outstanding substantive issues. On December 29, 2017, Examiner Kugel contacted Patentee's representative, Mr. Farsiou, telephonically to indicate that the Board's rationale does address such issues.

Claim Rejections – 35 U.S.C. §103

Claims 1-11 have been rejected under pre-AIA 35 U.S.C. §103(a) as allegedly being obvious over WO 2006/026395 ("the Keyser publication") in view of WO 02/053557 ("the Bolli publication").

In particular, the Examiner notes that the Keyser publication discloses methods of treating pulmonary hypertension comprising administering a PDE-5 inhibitor and an endothelin

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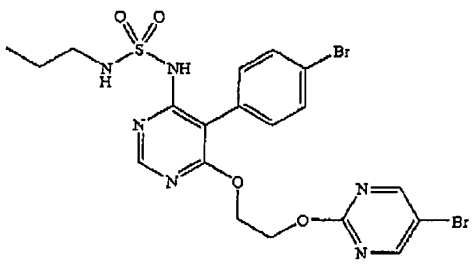
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(ET) receptor antagonist, but concedes that the Keyser publication does not disclose a compound of formula (I) as claimed (Office Action at 11). To address this deficiency, the Examiner cites the Bolli publication for its disclosure of the compound of formula (I) as an ET antagonist, and alleges that it would have been obvious to replace the Keyser publication's ET antagonist with the compound of formula (I) because the Bolli publication "teaches that they are functionally equivalent and are used for the same purpose" (*id.*).

Patentee respectfully requests that this rejection be reconsidered and withdrawn at least because – as the Board already found during prosecution of related patent applications – the claimed administration of a compound of Formula (I) and a PDE-5 inhibitor produces synergistic effects exceeding what those of ordinary skill in the art would have expected.

For example, during prosecution of the '148 application, the Board considered both the Keyser publication and the Bolli publication in relation to claims directed to methods of treating hypertension, pulmonary hypertension or pulmonary arterial hypertension comprising administering simultaneously, separately, or over a period of time, to a patient in need thereof, an effective amount of a compound of Formula (I):

(I)



in free or pharmaceutically acceptable salt form, and at least one compound having PDE-5-inhibitory properties, in free or pharmaceutically acceptable salt form. *See Ex parte Clozel*, Appeal 2014-009320 (Oct. 3, 2016) ("Decision"; attached as Exhibit A).

The Board reversed the rejection of claims 1-14 of the '148 application for obviousness over the Bolli publication in view of the Keyser publication (Exhibit A at 3). In doing so, the Board found, *inter alia*, that the Examiner did not adequately respond to Applicant's argument that the claimed inventions produce unexpectedly superior results (*id.*).

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UNITED THERAPEUTICS CORP., EX1003, page 303
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The Board also found that Applicant presented persuasive evidence that a person of ordinary skill would not have expected the synergistic effects produced by the administration of the compound of Formula (I) and a PDE-5 inhibitor (*id.* at 9; *see* the 847 Patent at col. 6 to col. 7, Examples 1-3). For example, the Board noted that the compound of Formula (I) is a dual ET_A-ET_B (*i.e.*, nonselective) inhibitor, and the Keyser publication teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects" (*id.* at 9, citing the Keyser publication at ¶ 67).

Specifically, the Keyser publication was said to teach that ET_A causes vasoconstriction such that the administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension (*id.* at 9, citing the Keyser publication at ¶ 68). The Board further noted that ET_B, on the other hand, was said to cause vasodilation wherein ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP (cyclic guanosine monophosphate) levels (*id.* at 10, citing the Keyser publication at ¶ 68). The Board noted that the Keyser publication further discloses that cGMP relaxes blood vessels, but PDE-5 breaks down cGMP (*id.*). The Keyser publication also discloses that administration of a PDE-5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE-5 antagonist (*id.*). Conversely, the Keyser publication explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production" (*id.*).

Based on this description, the Board found that those of ordinary skill would not have expected the administration of a nonselective ET antagonist, such as the compound of Formula (I), and a PDE-5 antagonist to produce the synergistic results reported in Applicant's specification (*id.*). In fact, the Board stated that "[i]f anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser" (*id.*, citing the Keyser publication at ¶¶68-69). For these reasons, the Board reversed the rejections of claims 1-14 for

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obviousness over the Bolli publication in view of the Keyser publication due to lack of supporting evidence (*id.*).[1]

For at least the reasons that the Board identified in reversing the then-pending obviousness rejection in the '148 application, Patentee requests reconsideration and withdrawal of the present §103 rejection.

Claims 1-11 have also been rejected under pre-AIA 35 USC §103(a) as being obvious over WO 2006/026395 ("the Keyser publication") in view of U.S. Patent No. 7,094,781 ("the '781 patent"). Patentee notes, however, that the '781 patent is the U.S. national stage of the International patent application corresponding to the Bolli publication (*i.e.*, PCT/EP01/14182). Given the substantive identity of the '781 patent and the Bolli publication, Patentee requests reconsideration and withdrawal of the rejection for at least the same reasons as noted above.

Claim Rejections – Double Patenting

Claims 1-11 have been rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of the '781 patent in view of the Keyser publication.

This rejection, however, is improper for at least the same reasons that the above-noted rejections under §103 are improper. Indeed, during prosecution of the '148 application, the Board addressed a rejection of similar claims for alleged non-statutory obviousness-type double patenting over the '781 patent in view of the Keyser publication (*see* Exhibit A at 3, 11). In reversing that rejection, the Board noted that "neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan" (*id.* at 11). For at least these reasons, Patentee requests reconsideration and withdrawal of the rejection.

[1] The Examiner presented similar rejections during prosecution of Application No. 14/162,280 but withdrew them in view of the Board Decision in the '148 application (*see* Office Action mailed December 29, 2016, at page 2).

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Claims 1-11 are also rejected on the ground of non-statutory obviousness-type double patenting over claims 1-16 of U.S. Patent No. 8,367,685 ("the '685 patent") as evidenced by the Bolli publication in view of the Keyser publication. But this rejection also is inconsistent with the Board's prior findings. The Board, for example, reversed a non-statutory obviousness-type double patenting rejection against the '148 application claims over claims of the '685 patent in view of the Bolli publication and the Keyser publication, noting that "neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan" (Exhibit A at 11). For at least these reasons, Patentee requests reconsideration and withdrawal of the rejection.

Conclusion

Patentee requests reconsideration and withdrawal of the rejections, and confirmation of the patentability, of claims 1-11 and allowance of new dependent claims 12-57. If the Examiner is of a contrary view or if issues remain, the Examiner is requested to contact the undersigned attorney at (215) 568-3100.

Date: January 16, 2018

/Joseph Lucci/
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EXHIBIT A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC	5499

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EXAMINER	
CARTER, KENDRA D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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PTOL-90A (Rev. 04/07)

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARTINE CLOZEL

Appeal 2014-009320
Application 13/604,148[1]
Technology Center 1600

Before LORA M. GREEN, FRANCISCO C. PRATS, and KRISTI L. R. SAWERT, *Administrative Patent Judges.*

SAWERT, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1–14 of U.S. Patent Application No. 13/604,148 ("the '148 application"). We have jurisdiction under 35 U.S.C. § 6(b).

[1] Appellants identify Actelion Pharmaceuticals Ltd. as the real party in interest. Appeal Br. 2.

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STATEMENT OF THE CASE

Claims 1–14 are on appeal and stand rejected as unpatentable under 35 U.S.C. § 103(a) over Bolli[2] in view of Keyser[3]. Final Off. Act. 11. Claims 1–14 also stand rejected on the ground of non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781[4] in view of Bolli and Keyser. *Id.* at 3–5. The Examiner has also provisionally rejected claims 1–14 on the ground of non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142[5] in view of Bolli and Keyser, *id.* at 6–8, and over claims 1–11 of Clozel '847[6] in view of Bolli and Keyser, *id.* at 8–10.

Claim 1 is illustrative of the claims on appeal. Claim 1 provides:

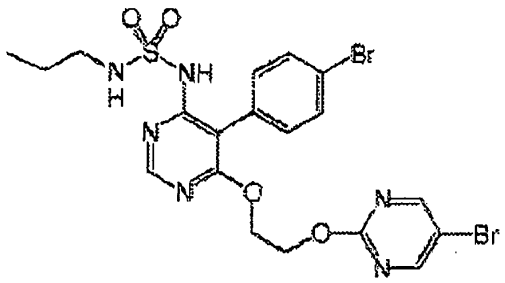
> 1. A method for the treatment of hypertension, pulmonary hypertension or pulmonary arterial hypertension, comprising administering simultaneously, separately or over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

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[2] Martin Bolli et al., WO 02/053557 A1 (published July 11, 2002) ("Bolli").
[3] Donald Keyser and Richard Dixon, WO 2006/026395 A1 (published March 9, 2006) ("Keyser").
[4] Martin Bolli et al., U.S. Patent No. 7,094,781 B2 (issued August 22, 2006) ("Bolli '781").
[5] Charles Tokunbo Adesuyi, U.S. Application No. 12/388,142 (filed Feb. 18, 2009) (issued as U.S. Patent No. 8,367,685 B2 on February 5, 2013) ("Adesuyi '142").
[6] Martine Clozel, U.S. Patent No. 8,268,847 B2 (issued September 18, 2012) ("Clozel '847").

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(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

Appeal Br. 12.

DISCUSSION

We have reviewed Appellant's arguments in the Briefs, the Examiner's Final Office Action, and the Examiner's Answer to the Appellant's arguments. Although we find that the Examiner made an adequate prima facie case of obviousness, we also find that the Examiner did not adequately respond to Appellant's argument that the claimed invention produces unexpectedly superior results. Thus, we reverse the rejection of claims 1–14 for obviousness over Bolli in view of Keyser, for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser. However, because the unexpectedly superior results do not apply to

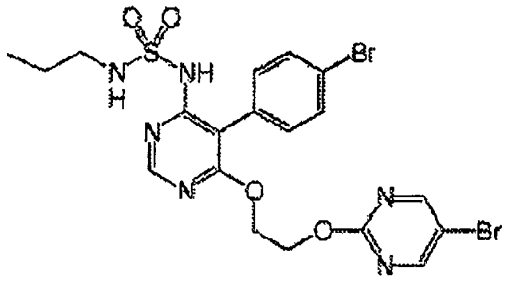
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the Examiner's rejection of claims 1–11 of Clozel '847 in view of Bolli and Keyser, we affirm this rejection.

Background

The subject matter disclosed in the '148 application relates to a pharmaceutical product comprising the compound of formula (I):



(I)

in combination with at least one compound having PDE5[7]-inhibitory properties. Spec. 1. The Specification teaches that the compound of formula (I) is a known endothelin-receptor antagonist useful for the treatment of various diseases involving vasoconstriction (e.g., heart failure, angina pectoris, pulmonary and systemic hypertension, and erectile dysfunction). *Id.* In addition, the Specification teaches that pyrazolopyrimidinone derivatives (e.g., sildenafil, vardenafil, tadalafil, and udenafil) are known PDE5 inhibitors also useful for the treatment of the same vasoconstriction-related diseases. *Id.*

[7] PDE5 stands for cyclic guanosine 3', 5'-monophosphate (cGMP) phosphodiesterase type 5. Spec. 2.

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The Specification states that the claimed invention is based on the "surprising[]" finding "that the combination of the compound of formula (I) with a compound having PDE5-inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved." *Id.* at 2. In test Example 1, for example, the administration of a compound of formula (I) decreased blood pressure with an ABC ("area above the curve") of 256, and the administration of tadalafil decreased blood pressure with an ABC of 310. But, the administration of a combination of a compound of formula (I) and tadalafil decreased blood pressure with an ABC of 923, which the Specification describes as a "synergistic effect." *Id.* at 9; *see also id.* at 9–10 (Examples 2 and 3).

The Examiner rejected claims 1–14 for obviousness over Bolli in view of Keyser. Final Off. Act. 11. Bolli discloses pyrimidine-sulfamides of the general formula I. Bolli 12–14. Of those compounds, Bolli specifically discloses the compound of formula (I) presently claimed in the '148 application. *See id.* at 28 (top right-hand corner). Bolli teaches that the compounds act as endothelin-receptor antagonists, *id.* at 1, useful "for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin," such as hypertension and pulmonary hypertension, *id.* at 11. Moreover, Bolli teaches that the compounds of general formula I "may also be used in combination with one or more other therapeutically useful substances," such as α- and β-blockers, vasodilators, calcium-antagonists, ACE-inhibitors, potassium activators, angiotensin II receptor antagonists, diuretics, sympatholitics, "and other therapeutics which serve to treat high blood pressure or any cardiac disorders." *Id.* at 17.

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Bolli does not specifically teach that the "other therapeutics" may be PDE5 inhibitors. Final Off. Act. 12. The Examiner relied on Keyser to make up for this deficiency. Keyser discloses "combination therapies" comprising an endothelin A receptor (ET_A)[8] antagonist and a PDE5 inhibitor for the treatment and prevention of cardiac disorders such as pulmonary arterial hypertension. Keyser (Abstract). Keyser specifically identifies sildenafil, tadalafil, vardenafil, and dasantafil as PDE5 inhibitors. *Id.* ¶ 29. Keyser also lists several known peptide and nonpeptidic ET_A antagonists, including: "cyclic peptides, acyltripeptides, hexapeptide analogs, certain anthraquinone derivatives, indanecarboxylic acids, certain N-pyrimidinylbenzenesulfonamides, certain benzenesulfonamides, and certain naphthalenesulfonamides." *Id.* ¶ 48. Finally, Keyser teaches that the ET_A antagonist and PDE5 inhibitor may be administered together in a "dual drug tablet[]," or in "separate dosage formulations so that each may be administered substantially concurrently or [] sequentially to provide required therapeutic amounts." *Id.* ¶ 32.

Keyser does not identify the compound of formula (I) presently claimed in the '148 application. However, the Examiner argued that it would have been obvious to

> combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary arterial hypertension, because the compound of Formula I is a ET antagonist, and Keyser et al. teach that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be

[8] There are two types of endothelin receptors: endothelin A (ET_A) and endothelin B (ET_B). ET_A is predominant in cardiovascular tissues. Keyser ¶ 12.

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combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

Final Off. Act. 13.

Analysis

A.

We agree with the Examiner that it would have been prima facie obvious to administer the compound of formula (I) as disclosed in Bolli and a PDE5 antagonist as taught by Keyser to treat hypertension.[9] Accordingly, we adopt the Examiner's fact findings and rationales provided in pages 11–13 of the Final Office Action. Where we disagree, however, is with the Examiner's treatment of Appellant's alleged unexpectedly superior results.

It is well established that "the prima facie case is merely a procedural device that enables an appropriate shift of the burden of production" from the examiner to the applicant. *Hyatt v. Dudas*, 492 F.3d 1365, 1369 (Fed. Cir. 2007). Here, the Appellant responds to the prima facie case with evidence of unexpectedly superior results. "After evidence or argument is

[9] For the sake of completeness, we note that Appellant's extensive "lead compound" arguments are inapposite to this case because the compound of formula (I) is not novel. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) ("We have held that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of adequate support in the prior art for the change in structure." (citations and quotations omitted)).

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submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Indeed, "[i]n reviewing the examiner's decision on appeal, the Board must necessarily weigh all of the evidence and argument." *Id.*

Upon reviewing the evidence of record, we find that Appellant submitted persuasive evidence of unexpectedly superior results that the Examiner did not adequately rebut. Specifically, Appellant found that the administration of the compound of formula (I) and a PDE5 antagonist decreased blood pressure in an amount much greater than either compound alone, thus producing a synergistic effect. Spec. 9–10 (Examples 1–3). In the case of synergistic effects, the "key question" as to obviousness is whether the combination of the compound of formula (I) and a PDE5 antagonist "proved more effective than what *would have been expected* in view of the prior art." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351–52 (Fed. Cir. 2013) (emphasis added). Here, the Examiner's response to Appellant's assertion of unexpected results consists of the following:

> With regard to the unexpected and synergistic results, the Examiner has considered the results and still does not find it persuasive to overcome the rejections of record because of the reasons above. Particularly, a combination of an ET antagonist and a PDE5 inhibitor is taught. There is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog (closest tested compound of art) taught by Bolli et al. for instance. Therefore the Applicant's arguments are non-persuasive to overcome the 35 U.S.C. 103(a) and obviousness type double patenting rejections of record.

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Ans. 14.

The Examiner refers to the N-ethyl analog of the compound of formula (I) disclosed in Bolli, and appears to imply that Appellant had a burden to test the effectiveness of that compound in combination with a PDE5 inhibitor. We disagree; the combination of the N-ethyl analog and a PDE5 inhibitor does not exist in the prior art. "It is not required that the claimed invention be compared with subject matter that does not exist in the prior art. The applicant is not required to create prior art, nor to prove that his invention would have been obvious if the prior art were different than it actually was." *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (Newman, J. concurring). Thus, we find that the Examiner has not persuasively showed by a preponderance of the evidence that Appellant's synergistic effects would have been expected from the prior art.

Moreover, we find that Appellant has presented persuasive evidence that an ordinarily skilled artisan would not have expected the synergistic effects produced by the administration of the compound of formula (I) and a PDE5 inhibitor. The compound of formula (I) is a dual ET_A-ET_B (i.e., nonselective) inhibitor. Appeal Br. 8–9. Keyser teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects." Keyser ¶ 67.

Specifically, Keyser explains that ET_A causes vasoconstriction. *Id.* at ¶ 68. Thus, administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension.

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ET_B, on the other hand, causes vasodilation. *Id.* ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP[10] levels. *Id.* cGMP relaxes blood vessels, but PDE5 breaks down cGMP. *Id.* Administration of a PDE5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE5 antagonist. *Id.* Conversely, Keyser explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production." *Id.*

Based on this description, we find that an ordinarily skilled artisan would not have expected the administration of a nonselective ET antagonist, such as the compound of formula (I), and a PDE5 antagonist to have produced the synergistic results provided in Appellant's Specification. If anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser. *See* Keyser ¶¶ 68–69. For these reasons, we determine that the Examiner's rejection of claims 1–14 for obviousness over Bolli in view of Keyser is unsupported by a preponderance of the evidence and therefore we reverse this rejection.

[10] cGMP stands for cyclic guanosine monophosphate.

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B.

For the same reasons, we also determine that the Examiner's rejections of claims 1–14 for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser, lack support by a preponderance of the evidence. Like Bolli, both Bolli '781 and Adesuyi '142 teach the compound of formula (I). But neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan. Thus, we reverse these non-statutory obviousness-type double patenting rejections.

C.

Finally, we affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. Clozel '847 teaches a method for treating hypertension or pulmonary hypertension by administering an effective amount of the compound of formula (I) in combination with a PDE5 inhibitory compound. *See, e.g.*, Clozel '847 (col. 8, ll. 29–35); *see also* Final Off. Act. 8–10. But, as Appellant notes, the '148 application is a continuation of the application leading to the '847 patent, Appeal Br. 11, and therefore is not prior art to the present application. We agree with the Examiner that a non-statutory obviousness-type double patenting rejection is appropriate in this case because representative claim 1 is not patentably distinct from the claims of

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Clozel '847. Specifically, representative claim 1 would be anticipated[11] by the claims of Clozel '847, but for the fact that Clozel '847 is not prior art. *In re Goodman*, 11 F.3d 1046, 1052–53 (Fed. Cir. 1993). Appellant makes no argument against the merits of this rejection. Therefore, we affirm.

SUMMARY

We affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. We reverse all other standing rejections.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

[11] Specifically, Clozel '847 discloses all elements of representative claim 1, except for the treatment of "pulmonary arterial hypertension." Final Off. Act. 8–9. But because representative claim 1 recites pulmonary arterial hypertension in the alternative (i.e., "the treatment of hypertension, pulmonary hypertension *or* pulmonary arterial hypertension"), Clozel '847 anticipates. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art.").

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Date: January 16, 2018 **Pages (including cover sheet):** 28

Name	Company	Fax #	Phone #
Examiner Timothy J. Kugel and Reexamination	United States Patent and Trademark Office	571-273-8300 and 571-273-9900	

From: David N. Farsiou
Client Matter #: 103693.000585
Re: In re Reexamination of Martine CLOZEL
Control No. 96/000,237
Filing Date: September 22, 2017
Confirmation No. 5019
Group Art Unit 3391
Examiner: Timothy J. Kugel

Message:

Attached hereto are the following documents for filing via facsimile:

Amendment In Ex Parte Reexamination Pursuant to 37 CFR 1.550 and 37 CFR 1.111 with facsimile certification (12 pages)

Exhibit A - Ex parte Clozel, Appeal 2014-009320 (Oct. 3, 2016) ("Decision") (14 pages)

Fee Transmittal (1)

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Fax Cover Sheet

Date: January 16, 2018 **Pages (including cover sheet):** 28

Name	Company	Fax #	Phone #
Examiner Timothy J. Kugel and Reexamination	United States Patent and Trademark Office	571-273-8300 and 571-273-9900	

From: David N. Farsiou
Client Matter #: 103693.000585
Re: In re Reexamination of Martine CLOZEL
Control No. 96/000,237
Filing Date: September 22, 2017
Confirmation No. 5019
Group Art Unit 3391
Examiner: Timothy J. Kugel

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CENTRAL REEXAMINATION UNIT

DOCKET NO.: 103693.000585 PATENT
Control No.: 96/000,237
Office Action Dated: November 13, 2017

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reexamination of:

Martine CLOZEL

Control No.: 96/000,237

Filing Date: September 22, 2017

Patent No.: 8,268,847

Confirmation No.: 5019

Group Art Unit: 3991

Examiner: Timothy J. Kugel

Therapeutic Compositions Comprising A Specific Endothelin Receptor Antagonist And A PDE5 Inhibitor

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AMENDMENT IN EX PARTE REEXAMINATION PURSUANT TO 37 CFR § 1.550 AND 37 C.F.R. § 1.111

In response to the Official Action dated November 13, 2017, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

☐ **Amendments to the Specification** begin on page of this paper.

☐ **Amendments to the Abstract** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.

☒ **Remarks** begin on page 8 of this paper.

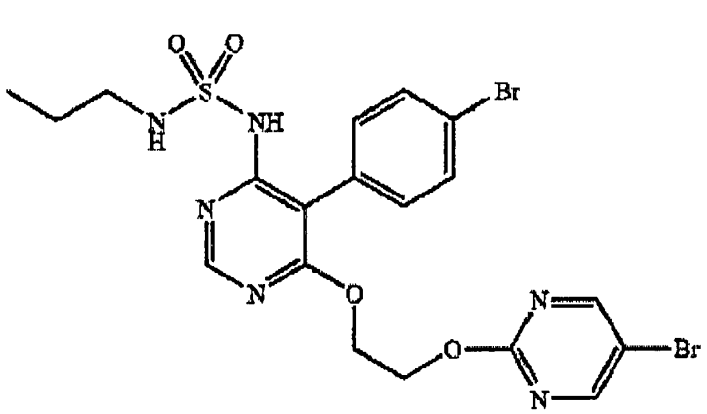
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U.S. PATENT 8,268,847

Listing of Claims:

1. A product containing the compound of formula (I) below:



(I)

in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

2. The product according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

3. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is tadalafil.

4. The product according to claim 2, wherein the compound having PDE5-inhibitory properties is sildenafil.

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U.S. PATENT 8,268,847

5. The product according to claim 1, wherein the disease wherein vasoconstriction is involved is selected from hypertension, pulmonary hypertension, diabetic arteriopathy, heart failure, erectile dysfunction and angina pectoris.

6. A pharmaceutical composition containing, as active principles, the compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form, as well as at least one excipient.

7. The pharmaceutical composition according to claim 6, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is tadalafil.

9. The pharmaceutical composition according to claim 7, wherein the compound having PDE5-inhibitory properties is sildenafil.

10. A method for the treatment of hypertension or pulmonary hypertension comprising administering to a patient in need thereof an effective amount of a compound of formula (I) as described in claim 1, in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

11. The method according to claim 10, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

12. (New) The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. (New) The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.

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14. (New) The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. (New) The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. (New) The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. (New) The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

18. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. (New) The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.

21. (New) The method of claim 20, wherein the interval between the administration of the compound of formula (I) and the administration of tadalafil does not exceed two days.

22. (New) The method of claim 21, wherein the interval does not exceed one day.

23. (New) The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

24. (New) The method of claim 23, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

25. (New) The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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26. (New) The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

27. (New) The method of claim 26, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

28. (New) The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

29. (New) The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

30. (New) The method of claim 29, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

31. (New) The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

32. (New) The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

33. (New) The method of claim 32, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

34. (New) The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

35. (New) The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

36. (New) The method of claim 35, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

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37. (New) The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

38. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. (New) The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

41. (New) The method of claim 40, wherein the interval between the administration of the compound of formula (I) and the administration of sildenafil does not exceed two days.

42. (New) The method of claim 41, wherein the interval does not exceed one day.

43. (New) The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

44. (New) The method of claim 43, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

45. (New) The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

46. (New) The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

47. (New) The method of claim 46, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

48. (New) The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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49. (New) The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

50. (New) The method of claim 49, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

51. (New) The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

52. (New) The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

53. (New) The method of claim 52, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

54. (New) The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

55. (New) The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

56. (New) The method of claim 55, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

57. (New) The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

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REMARKS

Following entry of the present amendments, claims 1-57 will be pending in this *ex parte* reexamination of U.S. Patent No. 8,268,847 ("the 847 Patent"). Claims 1-11 are original claims. New claims 12-57 are being added herein.

Support for the new claims may be found at, for example, the originally filed claims and col. 2, lines 36-39, col. 4, lines 25-28 (pulmonary arterial hypertension); col. 2, lines 15-35, col. 3, lines 36-57 (administration); and col. 4, lines 7-18 (dosage amounts) of the 847 Patent.

The new claims are patentable for at least the same reasons as the claims from which they depend.

Examiner Interview Summary

Patentee's undersigned counsel would like to thank the Central Reexamination Unit panel for the interview on December 20, 2017. The panel included examiners Timothy Kugel, Dwayne Jones, and Kendra Carter, and supervisory examiner Jean Witz. David Farsiou and the undersigned attended on behalf of Patentee. Patentee agrees with the summary reflected in the Applicant Initiated Interview Summary, dated December 27, 2017, namely that the panel agreed to review the Patent Trial and Appeal Board ("Board") decision rendered in Application No. 13/604,148 ("the '148 application") to determine whether making an argument consistent with the Board decision would address the outstanding substantive issues. On December 29, 2017, Examiner Kugel contacted Patentee's representative, Mr. Farsiou, telephonically to indicate that the Board's rationale does address such issues.

Claim Rejections – 35 U.S.C. §103

Claims 1-11 have been rejected under pre-AIA 35 U.S.C. §103(a) as allegedly being obvious over WO 2006/026395 ("the Keyser publication") in view of WO 02/053557 ("the Bolli publication").

In particular, the Examiner notes that the Keyser publication discloses methods of treating pulmonary hypertension comprising administering a PDE-5 inhibitor and an endothelin

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U.S. PATENT 8,268,847

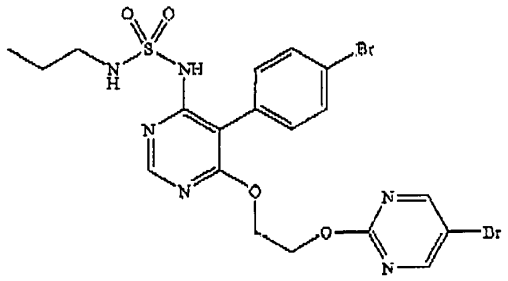
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(ET) receptor antagonist, but concedes that the Keyser publication does not disclose a compound of formula (I) as claimed (Office Action at 11). To address this deficiency, the Examiner cites the Bolli publication for its disclosure of the compound of formula (I) as an ET antagonist, and alleges that it would have been obvious to replace the Keyser publication's ET antagonist with the compound of formula (I) because the Bolli publication "teaches that they are functionally equivalent and are used for the same purpose" (*id.*).

Patentee respectfully requests that this rejection be reconsidered and withdrawn at least because – as the Board already found during prosecution of related patent applications – the claimed administration of a compound of Formula (I) and a PDE-5 inhibitor produces synergistic effects exceeding what those of ordinary skill in the art would have expected.

For example, during prosecution of the '148 application, the Board considered both the Keyser publication and the Bolli publication in relation to claims directed to methods of treating hypertension, pulmonary hypertension or pulmonary arterial hypertension comprising administering simultaneously, separately, or over a period of time, to a patient in need thereof, an effective amount of a compound of Formula (I):

(I)



in free or pharmaceutically acceptable salt form, and at least one compound having PDE-5-inhibitory properties, in free or pharmaceutically acceptable salt form. *See Ex parte Clozel*, Appeal 2014-009320 (Oct. 3, 2016) ("Decision"; attached as Exhibit A).

The Board reversed the rejection of claims 1-14 of the '148 application for obviousness over the Bolli publication in view of the Keyser publication (Exhibit A at 3). In doing so, the Board found, *inter alia*, that the Examiner did not adequately respond to Applicant's argument that the claimed inventions produce unexpectedly superior results (*id.*).

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The Board also found that Applicant presented persuasive evidence that a person of ordinary skill would not have expected the synergistic effects produced by the administration of the compound of Formula (I) and a PDE-5 inhibitor (*id.* at 9; *see* the 847 Patent at col. 6 to col. 7, Examples 1-3). For example, the Board noted that the compound of Formula (I) is a dual ET_A-ET_B (*i.e.*, nonselective) inhibitor, and the Keyser publication teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects" (*id.* at 9, citing the Keyser publication at ¶ 67).

Specifically, the Keyser publication was said to teach that ET_A causes vasoconstriction such that the administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension (*id.* at 9, citing the Keyser publication at ¶ 68). The Board further noted that ET_B, on the other hand, was said to cause vasodilation wherein ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP (cyclic guanosine monophosphate) levels (*id.* at 10, citing the Keyser publication at ¶ 68). The Board noted that the Keyser publication further discloses that cGMP relaxes blood vessels, but PDE-5 breaks down cGMP (*id.*). The Keyser publication also discloses that administration of a PDE-5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE-5 antagonist (*id.*). Conversely, the Keyser publication explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production" (*id.*).

Based on this description, the Board found that those of ordinary skill would not have expected the administration of a nonselective ET antagonist, such as the compound of Formula (I), and a PDE-5 antagonist to produce the synergistic results reported in Applicant's specification (*id.*). In fact, the Board stated that "[i]f anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser" (*id.*, citing the Keyser publication at ¶¶68-69). For these reasons, the Board reversed the rejections of claims 1-14 for

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obviousness over the Bolli publication in view of the Keyser publication due to lack of supporting evidence (*id.*).[1]

For at least the reasons that the Board identified in reversing the then-pending obviousness rejection in the '148 application, Patentee requests reconsideration and withdrawal of the present §103 rejection.

Claims 1-11 have also been rejected under pre-AIA 35 USC §103(a) as being obvious over WO 2006/026395 ("the Keyser publication") in view of U.S. Patent No. 7,094,781 ("the '781 patent"). Patentee notes, however, that the '781 patent is the U.S. national stage of the International patent application corresponding to the Bolli publication (*i.e.*, PCT/EP01/14182). Given the substantive identity of the '781 patent and the Bolli publication, Patentee requests reconsideration and withdrawal of the rejection for at least the same reasons as noted above.

Claim Rejections – Double Patenting

Claims 1-11 have been rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of the '781 patent in view of the Keyser publication.

This rejection, however, is improper for at least the same reasons that the above-noted rejections under §103 are improper. Indeed, during prosecution of the '148 application, the Board addressed a rejection of similar claims for alleged non-statutory obviousness-type double patenting over the '781 patent in view of the Keyser publication (*see* Exhibit A at 3, 11). In reversing that rejection, the Board noted that "neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan" (*id.* at 11). For at least these reasons, Patentee requests reconsideration and withdrawal of the rejection.

[1] The Examiner presented similar rejections during prosecution of Application No. 14/162,280 but withdrew them in view of the Board Decision in the '148 application (*see* Office Action mailed December 29, 2016, at page 2).

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Claims 1-11 are also rejected on the ground of non-statutory obviousness-type double patenting over claims 1-16 of U.S. Patent No. 8,367,685 ("the '685 patent") as evidenced by the Bolli publication in view of the Keyser publication. But this rejection also is inconsistent with the Board's prior findings. The Board, for example, reversed a non-statutory obviousness-type double patenting rejection against the '148 application claims over claims of the '685 patent in view of the Bolli publication and the Keyser publication, noting that "neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan" (Exhibit A at 11). For at least these reasons, Patentee requests reconsideration and withdrawal of the rejection.

Conclusion

Patentee requests reconsideration and withdrawal of the rejections, and confirmation of the patentability, of claims 1-11 and allowance of new dependent claims 12-57. If the Examiner is of a contrary view or if issues remain, the Examiner is requested to contact the undersigned attorney at (215) 568-3100.

Date: January 16, 2018

/Joseph Lucci/
Joseph Lucci
Registration No. 33307

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2929 Arch Street
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EXHIBIT A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC	5499

50446 7590 10/03/2016

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARTINE CLOZEL

Appeal 2014-009320
Application 13/604,148[1]
Technology Center 1600

Before LORA M. GREEN, FRANCISCO C. PRATS, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1–14 of U.S. Patent Application No. 13/604,148 ("the '148 application"). We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Appellants identify Actelion Pharmaceuticals Ltd. as the real party in interest. Appeal Br. 2.

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U.S. PATENT 8,268,847

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STATEMENT OF THE CASE

Claims 1–14 are on appeal and stand rejected as unpatentable under 35 U.S.C. § 103(a) over Bolli[2] in view of Keyser[3]. Final Off. Act. 11. Claims 1–14 also stand rejected on the ground of non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781[4] in view of Bolli and Keyser. *Id.* at 3–5. The Examiner has also provisionally rejected claims 1–14 on the ground of non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142[5] in view of Bolli and Keyser, *id.* at 6–8, and over claims 1–11 of Clozel '847[6] in view of Bolli and Keyser, *id.* at 8–10.

Claim 1 is illustrative of the claims on appeal. Claim 1 provides:

> 1. A method for the treatment of hypertension, pulmonary hypertension or pulmonary arterial hypertension, comprising administering simultaneously, separately or over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

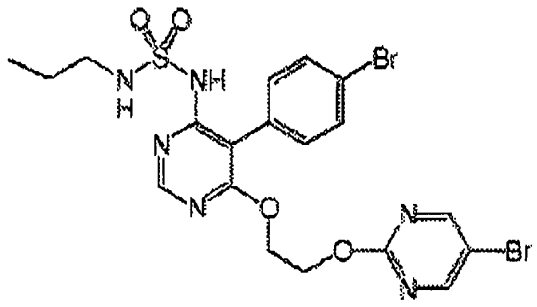
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[2] Martin Bolli et al., WO 02/053557 A1 (published July 11, 2002) ("Bolli").
[3] Donald Keyser and Richard Dixon, WO 2006/026395 A1 (published March 9, 2006) ("Keyser").
[4] Martin Bolli et al., U.S. Patent No. 7,094,781 B2 (issued August 22, 2006) ("Bolli '781").
[5] Charles Tokunbo Adesuyi, U.S. Application No. 12/388,142 (filed Feb. 18, 2009) (issued as U.S. Patent No. 8,367,685 B2 on February 5, 2013) ("Adesuyi '142").
[6] Martine Clozel, U.S. Patent No. 8,268,847 B2 (issued September 18, 2012) ("Clozel '847").

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(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

Appeal Br. 12.

DISCUSSION

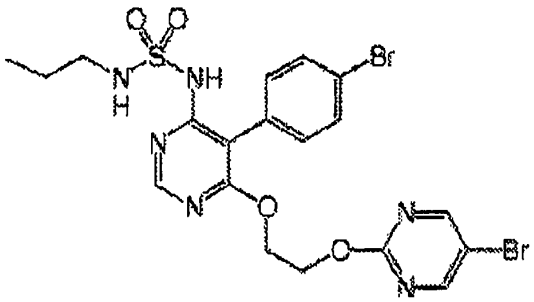
We have reviewed Appellant's arguments in the Briefs, the Examiner's Final Office Action, and the Examiner's Answer to the Appellant's arguments. Although we find that the Examiner made an adequate prima facie case of obviousness, we also find that the Examiner did not adequately respond to Appellant's argument that the claimed invention produces unexpectedly superior results. Thus, we reverse the rejection of claims 1–14 for obviousness over Bolli in view of Keyser, for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser. However, because the unexpectedly superior results do not apply to

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the Examiner's rejection of claims 1–11 of Clozel '847 in view of Bolli and Keyser, we affirm this rejection.

Background

The subject matter disclosed in the '148 application relates to a pharmaceutical product comprising the compound of formula (I):



(I)

in combination with at least one compound having PDE5[7]-inhibitory properties. Spec. 1. The Specification teaches that the compound of formula (I) is a known endothelin-receptor antagonist useful for the treatment of various diseases involving vasoconstriction (e.g., heart failure, angina pectoris, pulmonary and systemic hypertension, and erectile dysfunction). *Id.* In addition, the Specification teaches that pyrazolopyrimidinone derivatives (e.g., sildenafil, vardenafil, tadalafil, and udenafil) are known PDE5 inhibitors also useful for the treatment of the same vasoconstriction-related diseases. *Id.*

[7] PDE5 stands for cyclic guanosine 3', 5'-monophosphate (cGMP) phosphodiesterase type 5. Spec. 2.

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The Specification states that the claimed invention is based on the "surprising[]" finding "that the combination of the compound of formula (I) with a compound having PDE5-inhibitory properties results in an unexpected synergistic effect in the treatment of diseases wherein vasoconstriction is involved." *Id.* at 2. In test Example 1, for example, the administration of a compound of formula (I) decreased blood pressure with an ABC ("area above the curve") of 256, and the administration of tadalafil decreased blood pressure with an ABC of 310. But, the administration of a combination of a compound of formula (I) and tadalafil decreased blood pressure with an ABC of 923, which the Specification describes as a "synergistic effect." *Id.* at 9; *see also id.* at 9–10 (Examples 2 and 3).

The Examiner rejected claims 1–14 for obviousness over Bolli in view of Keyser. Final Off. Act. 11. Bolli discloses pyrimidine-sulfamides of the general formula I. Bolli 12–14. Of those compounds, Bolli specifically discloses the compound of formula (I) presently claimed in the '148 application. *See id.* at 28 (top right-hand corner). Bolli teaches that the compounds act as endothelin-receptor antagonists, *id.* at 1, useful "for treatment of diseases, which are associated with an increase in vasoconstriction, proliferation or inflammation due to endothelin," such as hypertension and pulmonary hypertension, *id.* at 11. Moreover, Bolli teaches that the compounds of general formula I "may also be used in combination with one or more other therapeutically useful substances," such as α- and β-blockers, vasodilators, calcium-antagonists, ACE-inhibitors, potassium activators, angiotensin II receptor antagonists, diuretics, sympatholitics, "and other therapeutics which serve to treat high blood pressure or any cardiac disorders." *Id.* at 17.

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Bolli does not specifically teach that the "other therapeutics" may be PDE5 inhibitors. Final Off. Act. 12. The Examiner relied on Keyser to make up for this deficiency. Keyser discloses "combination therapies" comprising an endothelin A receptor (ET_A)[8] antagonist and a PDE5 inhibitor for the treatment and prevention of cardiac disorders such as pulmonary arterial hypertension. Keyser (Abstract). Keyser specifically identifies sildenafil, tadalafil, vardenafil, and dasantafil as PDE5 inhibitors. *Id.* ¶ 29. Keyser also lists several known peptide and nonpeptidic ET_A antagonists, including: "cyclic peptides, acyltripeptides, hexapeptide analogs, certain anthraquinone derivatives, indanecarboxylic acids, certain N-pyrimidinylbenzenesulfonamides, certain benzenesulfonamides, and certain naphthalenesulfonamides." *Id.* ¶ 48. Finally, Keyser teaches that the ET_A antagonist and PDE5 inhibitor may be administered together in a "dual drug tablet[]," or in "separate dosage formulations so that each may be administered substantially concurrently or [] sequentially to provide required therapeutic amounts." *Id.* ¶ 32.

Keyser does not identify the compound of formula (I) presently claimed in the '148 application. However, the Examiner argued that it would have been obvious to

> combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary arterial hypertension, because the compound of Formula I is a ET antagonist, and Keyser et al. teach that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be

[8] There are two types of endothelin receptors: endothelin A (ET_A) and endothelin B (ET_B). ET_A is predominant in cardiovascular tissues. Keyser ¶ 12.

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combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

Final Off. Act. 13.

Analysis

A.

We agree with the Examiner that it would have been prima facie obvious to administer the compound of formula (I) as disclosed in Bolli and a PDE5 antagonist as taught by Keyser to treat hypertension.[9] Accordingly, we adopt the Examiner's fact findings and rationales provided in pages 11–13 of the Final Office Action. Where we disagree, however, is with the Examiner's treatment of Appellant's alleged unexpectedly superior results.

It is well established that "the prima facie case is merely a procedural device that enables an appropriate shift of the burden of production" from the examiner to the applicant. *Hyatt v. Dudas*, 492 F.3d 1365, 1369 (Fed. Cir. 2007). Here, the Appellant responds to the prima facie case with evidence of unexpectedly superior results. "After evidence or argument is

[9] For the sake of completeness, we note that Appellant's extensive "lead compound" arguments are inapposite to this case because the compound of formula (I) is not novel. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) ("We have held that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of adequate support in the prior art for the change in structure." (citations and quotations omitted)).

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submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Indeed, "[i]n reviewing the examiner's decision on appeal, the Board must necessarily weigh all of the evidence and argument." *Id.*

Upon reviewing the evidence of record, we find that Appellant submitted persuasive evidence of unexpectedly superior results that the Examiner did not adequately rebut. Specifically, Appellant found that the administration of the compound of formula (I) and a PDE5 antagonist decreased blood pressure in an amount much greater than either compound alone, thus producing a synergistic effect. Spec. 9–10 (Examples 1–3). In the case of synergistic effects, the "key question" as to obviousness is whether the combination of the compound of formula (I) and a PDE5 antagonist "proved more effective than what *would have been expected* in view of the prior art." *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1351–52 (Fed. Cir. 2013) (emphasis added). Here, the Examiner's response to Appellant's assertion of unexpected results consists of the following:

> With regard to the unexpected and synergistic results, the Examiner has considered the results and still does not find it persuasive to overcome the rejections of record because of the reasons above. Particularly, a combination of an ET antagonist and a PDE5 inhibitor is taught. There is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog (closest tested compound of art) taught by Bolli et al. for instance. Therefore the Applicant's arguments are non-persuasive to overcome the 35 U.S.C. 103(a) and obviousness type double patenting rejections of record.

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Ans. 14.

The Examiner refers to the N-ethyl analog of the compound of formula (I) disclosed in Bolli, and appears to imply that Appellant had a burden to test the effectiveness of that compound in combination with a PDE5 inhibitor. We disagree; the combination of the N-ethyl analog and a PDE5 inhibitor does not exist in the prior art. "It is not required that the claimed invention be compared with subject matter that does not exist in the prior art. The applicant is not required to create prior art, nor to prove that his invention would have been obvious if the prior art were different than it actually was." *In re Geiger*, 815 F.2d 686, 690 (Fed. Cir. 1987) (Newman, J. concurring). Thus, we find that the Examiner has not persuasively showed by a preponderance of the evidence that Appellant's synergistic effects would have been expected from the prior art.

Moreover, we find that Appellant has presented persuasive evidence that an ordinarily skilled artisan would not have expected the synergistic effects produced by the administration of the compound of formula (I) and a PDE5 inhibitor. The compound of formula (I) is a dual ET_A-ET_B (i.e., nonselective) inhibitor. Appeal Br. 8–9. Keyser teaches that "[u]se of a nonselective ET receptor [inhibitor] interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complementary fashion for the multiple pathways (PDE and/or prostacyclin and/or ET_A) to provide superior efficacy and/or dosage regimes and/or reduction in side effects." Keyser ¶ 67.

Specifically, Keyser explains that ET_A causes vasoconstriction. *Id.* at ¶ 68. Thus, administration of an ET_A antagonist results in less vasoconstriction, which in turn ameliorates the symptoms of hypertension.

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ET_B, on the other hand, causes vasodilation. *Id.* ET_B-mediated vasodilation occurs through a series of steps leading to an increase in cGMP[10] levels. *Id.* cGMP relaxes blood vessels, but PDE5 breaks down cGMP. *Id.* Administration of a PDE5 antagonist prevents the breakdown of cGMP, thus leading to "increased vasodilation and better efficacy of both" the ET_A antagonist and the PDE5 antagonist. *Id.* Conversely, Keyser explains, "[n]onselective antagonists would not function as effectively because they block the ET_B stimulated cGMP production." *Id.*

Based on this description, we find that an ordinarily skilled artisan would not have expected the administration of a nonselective ET antagonist, such as the compound of formula (I), and a PDE5 antagonist to have produced the synergistic results provided in Appellant's Specification. If anything, the skilled artisan most likely would have expected inferior results based on the discussion in Keyser. *See* Keyser ¶¶ 68–69. For these reasons, we determine that the Examiner's rejection of claims 1–14 for obviousness over Bolli in view of Keyser is unsupported by a preponderance of the evidence and therefore we reverse this rejection.

[10] cGMP stands for cyclic guanosine monophosphate.

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B.

For the same reasons, we also determine that the Examiner's rejections of claims 1–14 for non-statutory obviousness-type double patenting over claims 8 and 9 of Bolli '781 in view of Bolli and Keyser, and for non-statutory obviousness-type double patenting over claims 1, 9, 10, and 18 of Adesuyi '142 in view of Bolli and Keyser, lack support by a preponderance of the evidence. Like Bolli, both Bolli '781 and Adesuyi '142 teach the compound of formula (I). But neither reference teaches or suggests that the synergistic results obtained from the presently claimed invention would have been expected to an ordinarily skilled artisan. Thus, we reverse these non-statutory obviousness-type double patenting rejections.

C.

Finally, we affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. Clozel '847 teaches a method for treating hypertension or pulmonary hypertension by administering an effective amount of the compound of formula (I) in combination with a PDE5 inhibitory compound. *See, e.g.*, Clozel '847 (col. 8, ll. 29–35); *see also* Final Off. Act. 8–10. But, as Appellant notes, the '148 application is a continuation of the application leading to the '847 patent, Appeal Br. 11, and therefore is not prior art to the present application. We agree with the Examiner that a non-statutory obviousness-type double patenting rejection is appropriate in this case because representative claim 1 is not patentably distinct from the claims of

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Clozel '847. Specifically, representative claim 1 would be anticipated[11] by the claims of Clozel '847, but for the fact that Clozel '847 is not prior art. *In re Goodman*, 11 F.3d 1046, 1052–53 (Fed. Cir. 1993). Appellant makes no argument against the merits of this rejection. Therefore, we affirm.

SUMMARY

We affirm the obviousness-type double patenting rejection of claims 1–14 over claims 1–11 of Clozel '847 in view of Bolli and Keyser. We reverse all other standing rejections.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

[11] Specifically, Clozel '847 discloses all elements of representative claim 1, except for the treatment of "pulmonary arterial hypertension." Final Off. Act. 8–9. But because representative claim 1 recites pulmonary arterial hypertension in the alternative (i.e., "the treatment of hypertension, pulmonary hypertension *or* pulmonary arterial hypertension"), Clozel '847 anticipates. *See Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art.").

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Fax Cover Sheet

Date: January 16, 2018 **Pages (including cover sheet):** 28

Name	Company	Fax #	Phone #
Examiner Timothy J. Kugel and Reexamination	United States Patent and Trademark Office	571-273-8300 and 571-273-9900	

From: David N. Farsiou
Client Matter #: 103693.000585
Re: In re Reexamination of Martine CLOZEL Confirmation No. 5019
Control No. 96/000,237 Group Art Unit 3391
Filing Date: September 22, 2017 Examiner: Timothy J. Kugel

Message:

Attached hereto are the following documents for filing via facsimile:

Amendment In Ex Parte Reexamination Pursuant to 37 CFR 1.550 and 37 CFR 1.111 with facsimile certification (12 pages)

Exhibit A - Ex parte Clozel, Appeal 2014-009320 (Oct. 3, 2016) ("Decision") (14 pages)

Fee Transmittal (1)

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Fee Transmittal (1) Re Fax'ng Fee Transmittal 1 page
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FEE TRANSMITTAL

	Complete if known
Application Number	96/000,237
Filing Date	September 22, 2017
First Named Inventor	Martine CLOZEL
Examiner Name	Timothy J. Kugel
Art Unit	3991
Practitioner Docket No.	103693.000585

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 3,700.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 233000 Deposit Account Name: Baker & Hostetler LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	U ($)	S ($)	M ($)	Fees Paid ($)
Utility	300	150*	75	660	330	165	760	380	190	
Design	200	100	50	160	80	40	600	300	150	
Plant	200	100	50	420	210	105	620	310	155	
Reissue	300	150	75	660	330	165	2,200	1,100	550	
Provisional	280	140	70	0	0	0	0	0	0	

* The $150 small entity status filing fee for a utility application is further reduced to $75 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	Undiscounted Fee ($)	Small Entity Fee ($)	Micro Entity Fee ($)
Each claim over 20 (including Reissues)	100	50	25
Each independent claim over 3 (including Reissues)	460	230	115
Multiple dependent claims	820	410	205

Total Claims		Extra Claims	Fee ($)		Fee Paid ($)
57	-20 or HP =	37 x	100	=	3,700.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
	-3 or HP =	0 x	0	=	0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $400 ($200 for small entity) ($100 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
	- 100 =		/ 50 =		(round up to a whole number) x		=	

4. OTHER FEE(S) Fees Paid ($)

Non-English specification, $130 fee (no small or micro entity discount)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)

Other (e.g., late filing surcharge): _____

SUBMITTED BY

Signature	/David N. Farsiou/	Registration No. (Attorney/Agent) 44,104	Telephone 215-568-3100
Name (Print/Type)	David N. Farsiou		Date January 16, 2018

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Fax Cover Sheet

Date: January 16, 2018 **Pages (including cover sheet):** 28

Name	Company	Fax #	Phone #
Examiner Timothy J. Kugel and Reexamination	United States Patent and Trademark Office	571-273-8300 and 571-273-9900	

From: David N. Farsiou
Client Matter #: 103693.000585
Re: In re Reexamination of Martine CLOZEL
Control No. 96/000,237
Filing Date: September 22, 2017
Confirmation No. 5019
Group Art Unit 3391
Examiner: Timothy J. Kugel

Message:

Attached hereto are the following documents for filing via facsimile:

Amendment In Ex Parte Reexamination Pursuant to 37 CFR 1.550 and 37 CFR 1.111 with facsimile certification (12 pages)

Exhibit A - Ex parte Clozel, Appeal 2014-009320 (Oct. 3, 2016) ("Decision") (14 pages)

Fee Transmittal (1)

If this transmission is not complete, please call David N. Farsiou at 215.564.8984.

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611917480.1

PAGE 1/28 * RCVD AT 1/16/2018 6:43:00 PM [Eastern Standard Time] * SVR:W-PTOFAX-002/17 * DNIS:2738900 * CSID: * DURATION (mm-ss):07-14

Doc Code: WFEE
Document Description: Fee Worksheet (PTO-875)

PTO/SB/06 (10-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number: 96/000237

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	x =		OR	x =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	x =			x =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT A — 1/16/18

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 57	Minus	** 20	= 37	x =		OR	x =	
Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

/MANUEL SALDANA/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Substitute for Form 1449/PTO	*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	**Application Number**	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
(use as many sheets as necessary)	**Examiner Name**	Kugel, Timothy J
	Attorney Docket Number	103693.000585

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document
	1	2005/0101608	05-12-2005	Santel
	2	2010/0004274	01-07-2010	Adesuyi et al.
	3	2011/0136818	06-09-2011	Clozel
	4	2013/0005734	01-03-2013	Clozel
	5	2013/0190336	07-25-2013	Adesuyi et al.
	6	2013/0310407	11-21-2013	Regenass et al.
	7	2013/0317048	11-28-2013	Clozel et al.
	8	2014/0148460	05-29-2014	Clozel
	9	2014/0329824	11-06-2014	Clozel
	10	6,458,805	10-01-2002	Blok et al.
	11	8,541,433	09-24-2013	Clozel et al.
	12	8,809,334	08-19-2014	Clozel
	13	9,173,881	11-03-2015	Clozel

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Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number -Kind Code (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T*
	14	JP 2005-504113	02-10-2005	Novartis Pharma GMBH		T
	15	WO 02/053557	07-11-2002	Actelion Pharmaceuticals Ltd.		
	16	WO 2003/028730	04-10-2003	Novartis AG		
	17	WO 2004/056787	07-08-2004	Pfizer Limited		
	18	WO 2005/112939	12-01-2005	Solvay Pharmaceuticals GMBH		

Substitute for Form 1449/PTO	*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	**Application Number**	96/000,237
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	First Named Inventor	8,268,847
	Art Unit	3991
(use as many sheets as necessary)	**Examiner Name**	Kugel, Timothy J
	Attorney Docket Number	103693.000585

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T*
	19	Letter from MSN Laboratories Private Limited to Actelion Pharmaceuticals Ltd. et al., December 19, 2017, pages 1-63, Redacted Version	
	20	Letter from Sun Pharma Global FZE to Actelion Pharmaceuticals, Ltd. et al., December 14, 2017, pages 1-59, Redacted Version	
	21	Letter from Teva Pharmaceuticals USA to Actelion Pharmaceuticals, Ltd. et al., December 20, 2017, 1-19, Redacted Version	
	22	Letter from Zydus Pharmaceuticals (USA) Inc. to Actelion Pharmaceuticals Ltd et al., December 19, 2017, pages 1-95, Redacted Version	
	23	Tracleer® [bosentan], NDA 21-290/S-006 and S-007, November 14, 2005, 20 pages	
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	26	BATTISTINI et al., "Profile of Past and Current Clinical Trials Involving Endothelin Receptor Antagonists: The Novel "-Sentan" Class of Drug", Exp. Biol. Med., (2006), Vol. 231(6), pg. 653-695.	
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	29	CLOZEL et al., "Bosentan, sildenafil, and their combination in the monocrotaline model of pulmonary hypertension in rats", Exp. Biol. Med (Maywood), 2006, 231(6), 967-973	
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	34	HOEPER et al., "Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension", Eur. Respir. J., 2004, 24, 1007-1010	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT	**Application Number**	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
(use as many sheets as necessary)	**Examiner Name**	Kugel, Timothy J
	Attorney Docket Number	103693.000585

NON PATENT LITERATURE DOCUMENTS			
	36	HOEPER, "Drug Treatment of Pulmonary Arterial Hypertension: current and future agents", Drugs, July 2005, 65(10), 1337-1354	
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	38	LEE et al., "Current treatment strategies for pulmonary arterial hypertension", J. Int. Med., 2005, 258, 199-215	
	39	LEVIN, "Anti-Hypertensive Drugs 1 The development of non-peptide angiotensin II receptor antagonists", (P. VanZwieten et al. ed., Harwood Academic Publishers), 1997, (e-Book), page 9	
	40	LUNZE et al., "First experience with an oral combination therapy using bosentan and sildenafil for pulmonary arterial hypertension", Eur. J. Clin. Invest, 2006, 36 (Suppl, 3), 32-38	
	41	MAGUIRE ET AL; "Defining the Affinity and Receptor Sub-type Selectivity of Four Classes of Endothelin Antagonists in Clinically Relevant Human Cardiovascular Tissues"; Life Sciences 91, (2012); 681-686	
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	46	PAUL et al., "Bosentan Decreases the Plasma Concentration of Sildenafil When Coprescribed in Pulmonary Hypertension", British Journal of Clinical Pharmacology, (2005), Vol. 60(1), pg. 107-112.	
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	48	PULIDO et al., "Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension", The New England Journal of Medicine, (2013), Vol. 369(9), pg. 809-818.	
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	50	SIMPSON et al., "Preliminary experience with bosentan as initial therapy in childhood idiopathic pulmonary arterial hypertension", J Heart Lung Transplant, 2006, 25(4), 469-473	
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Examiner Signature		**Date Considered**	

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*	*Complete if Known*	
	Application Number	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
	Examiner Name	Kugel, Timothy J
	Attorney Docket Number	103693.000585

CERTIFICATION STATEMENT

Please see 37 CFR § 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

CONTENT OF IDS

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

STATEMENT UNDER 37 C.F.R. § 1.704(d)(1)

☐ This information disclosure statement is in compliance with §§ 1.97 and 1.98 and will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs 37 C.F.R. § 1.704(c)(6), (c)(8), (c)(9), or (c)(10) because each item of information contained in the information disclosure statement:

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	Application Number	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
	Examiner Name	Kugel, Timothy J
	Attorney Docket Number	103693.000585

any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

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☐ See attached certification statement.

☐ The fee set forth in § 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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SIGNATURE

/Joseph Lucci/

Date: January 22, 2018

Joseph Lucci
Registration No. 33,307

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Facsimile: (215) 568-3439

Electronic Acknowledgement Receipt	
EFS ID:	31567075
Application Number:	96000237
International Application Number:	
Confirmation Number:	5019
Title of Invention:	THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR
First Named Inventor/Applicant Name:	8268847
Customer Number:	45511
Filer:	Joseph Lucci/Nicole Waeltz
Filer Authorized By:	Joseph Lucci
Attorney Docket Number:	
Receipt Date:	22-JAN-2018
Filing Date:	22-SEP-2017
Time Stamp:	15:04:18
Application Type:	Supplemental Examination
Patent Number:	

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Miscellaneous Incoming Letter	103693-000585_SIDS_1449_1-22-18.PDF	168860 30e9f739a9a644f57c4bf786fad7f8762a56dc90	no	5
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Information:					
2	Foreign Reference	JP_2005-504113wEngAbs.PDF	2953785 3b915914422e539f78f9960605a7537a87041f85	no	76
Warnings:					
Information:					
3	Foreign Reference	WO_02-053557A1.PDF	3967617 5346b04b6d17ee0f1dff21b3bfe37f34039b7e16	no	143
Warnings:					
Information:					
4	Foreign Reference	WO_2003-028730.PDF	1670155 3a0410cca9c13338b1b439088e4a6910ac10500a	no	38
Warnings:					
Information:					
5	Foreign Reference	WO_2004-056787.PDF	4251826 7c79f3cb314187c3fe011f8dc933fbdbe23c6a1d	no	109
Warnings:					
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6	Foreign Reference	WO_2005-112939.PDF	1480692 306db520ff425f704001665bfcf69dd6ec3a3257	no	34
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7	Non Patent Literature	Larner_MSNNoticeLetter_12-19-17_23pgs.PDF	20713961 3d1904e5f08587d05b331d80bd2ade2ac71ec4a6	no	23
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8	Non Patent Literature	SunNoticeLetter_12-14-17_24pgs.PDF	866481 b16df5d5fbe9bbe2ae23662873ea415c47cbeb55	no	24
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Warnings:					
Information:					
10	Non Patent Literature	ZydusNoticeLetter_12-19-17_31pgs.PDF	6702921 fbeba6d31ed847ecc88f2463f24e43044e6e2904	no	31
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11	Non Patent Literature	Tracleer_NDA21-29-S006-S007_11-14-05_20pgs.PDF	15398377 0b0366d793d0ca6cc4436194ce46e0deda880b71	no	20
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12	Non Patent Literature	Badesch_MedicalTherapy_2004_35s-62S.PDF	2135709 38e4b4c1f2019b132c48e14a3a2db8701fd00198	no	30
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13	Non Patent Literature	Barst_SitaxsentanTherapy_2004_441-447.PDF	7077781 607d690d69080ad6730817147f54562699bf8084	no	7
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Information:					
14	Non Patent Literature	Battistini_ProfileOfPast_2006_653-695.PDF	24766428 eac94d53eea9250a4998b5d9cd11f765410790ff	no	43
Warnings:					
Information:					

15	Non Patent Literature	Bolli_TheDiscoveryOfN_2012_7849-7861.PDF	12417965 139ee333b807fba48f0d99bcca2ec5bafbcd8ce2	no	13
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16	Non Patent Literature	Breu_InVitroCharacterization_1993_210-214.PDF	900187 58f385532e23fdad5f837ffc8a832747af663f2b	no	5
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17	Non Patent Literature	Clozel_BosentanSildenafil_2006_967-973.PDF	5738716 27aae4ba04217e310ad816fd461fa7459bf6b6c7	no	7
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18	Non Patent Literature	Galie_SildenafilCitrate_2005_2148-2157.PDF	8013815 c0af4bac9a89592d65e3720694764 0ead036ce8a	no	10
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19	Non Patent Literature	Gatfield_SlowReceptor_2012_1-10.PDF	13265976 26cf15b2004fdd895ef0ff23e0a0e09425a47573	no	11
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Information:					
20	Non Patent Literature	Hoeper_AdvancesInProstanoid_2006_1-8.PDF	1973056 ccd1e937c994b4321c5354c3d1e409da471a3479	no	4
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Information:					
21	Non Patent Literature	Hoeper_CombinationTherapy_2004_339-340.PDF	2277727 25a12bc49e712af66c6674fab7061960365d9e65	no	2
Warnings:					
Information:					

22	Non Patent Literature	Hoeper_CombinationTherpay_2004_1007-1010.PDF	5027645 45efcd20af863cec3c014061f102250c7e2a74f3	no	4
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23	Non Patent Literature	Hoeper_Goal-orientedTreatment_2005_858-863.PDF	6244645 fec607fafea24ea6f572467167l5a5c76fdd8de9	no	6
Warnings:					
Information:					
24	Non Patent Literature	Hoeper_DrugTreatment_2005_1337-1354.PDF	14863004 2c1fd786ce77c850e922cd88a7e7a15b6f62cd18	no	18
Warnings:					
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25	Non Patent Literature	Humbert_TreatmentOfPulmonary_2004_1425-1436.PDF	12119955 c955da996861967dcb5dc177e3c59b605050b31d	no	12
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26	Non Patent Literature	Lee_CurrentTreatment_2005_199-215.PDF	307681 508a7e568eb01a53c4884a51d945dfe9537e2729	no	17
Warnings:					
Information:					
27	Non Patent Literature	Levin_Anti-HypertensiveDrugs_1997_pg9.PDF	1274610 18c6b11beae196349bfe1692a2386d69ccb3f130	no	3
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28	Non Patent Literature	Lunze_FirstExperience_2006_32-38.PDF	7056226 edea2a503b425327a0413c5e211d25b05fa3ddb4	no	7
Warnings:					
Information:					

29	Non Patent Literature	Maguire_DefiningTheAffinity_2012_681-686.PDF	8943026 ea02cffdf7ff127784edc2632582cc629cf20171	no	6
Warnings:					
Information:					
30	Non Patent Literature	Minai_Long-termResults_2006_880-883.PDF	4044968 f3d1a24370a12db4a2c20c7edb46e8ed328b473a	no	4
Warnings:					
Information:					
31	Non Patent Literature	Morice_LetterToEditor_2005_1page.PDF	1129668 e1545c31d05fc4229b4b1cb02e312ae7df671708	no	1
Warnings:					
Information:					
32	Non Patent Literature	Oberlander_StructuralVariation_1991_581-586.PDF	10085126 b4716b3e2ef5faf30962d45eb146329555b87b70	no	6
Warnings:					
Information:					
33	Non Patent Literature	Opitz_InhibitionOfEndothelin_2008_1936-1948.PDF	12928079 5e1c9b871b24f612028a01125dd34cb2c06d2e50	no	13
Warnings:					
Information:					
34	Non Patent Literature	Paul_BoseentanDecreases_2005_107-112.PDF	5994665 cee39a6fe8216183c292545be66bda16a0ce4c38	no	6
Warnings:					
Information:					
35	Non Patent Literature	OpsumitUS_PrescribingInformation_2013_22pgs.PDF	13925081 160bc6972788701293d77e77c2e4510682f97d80	no	22
Warnings:					
Information:					

36	Non Patent Literature	Pulido_MacitentanAndMorbidity_2013_809-818.PDF	8628766 5a46f00d7ee248aae34932ef611e02c5b5a554f5	no	10
Warnings:					
Information:					
37	Non Patent Literature	Roark_BioisosterismInDrug_1995_29-39.PDF	1916748 c33dade984f414d5b6be567cb33da8ba8b8bcdf5	no	11
Warnings:					
Information:					
38	Non Patent Literature	Simpson_PreliminaryExperience_2006_469-473.PDF	5175860 19938b6b5448336194aa3f66c2d2475c6bb22674	no	5
Warnings:					
Information:					
39	Non Patent Literature	Wilkins_SildenafilVersusEndothelin_2005_1292-1297.PDF	162728 3aed4ba495c402001b81b3765b202ef38b48a93e	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	268562217	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Litigation Search Report CRU 3999

Reexam Control No. 96/000,237

TO: TIMOTHY KUGEL Location: CRU Art Unit: 3991 Date: 01/25/2018	From: MANUEL SALDANA Location: CRU 3999 MDE 5D14 Phone: (571) 272-7740 MANUEL.SALDANA@uspto.gov

Search Notes

Litigation was NOT found for US Patent Number: **8,268,847**

1) I performed a KeyCite Search in Westlaw, which retrieves all history on the patent including any litigation.

2) I performed a search on the patent in Lexis CourtLink for any open dockets or closed cases.

3) I performed a search in Lexis in the Federal Courts and Administrative Materials databases for any cases found.

4) I performed a search in Lexis in the IP Journal and Periodicals database for any articles on the patent.

5) I performed a search in Lexis in the news databases for any articles about the patent or any articles about litigation on this patent.

Patent Search 8268847 1/25/2018

No cases found.

Return to Search

(Charges for search still apply)

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Citing References (15)

Treatment	Title	Date	Type	Depth	Headnote(s)
Examined by	**1. EX PARTE MARTINE CLOZEL** 2016 WL 5787594, *1+ , Patent Tr. & App. Bd. This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1-14 of U.S. Patent Application No. 13/604,148 (''the '148 application''). We have jurisdiction under 35 U.S.C....	Sep. 29, 2016	Administrative Decision		—
Discussed by	**2. Appeal Brief Under 37 C.F.R. s 41.37** Out Of Plan Ex Parte Martine Clozel. 2013 WL 12123481, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	Dec. 27, 2013	Administrative Filing		—
Cited by	**3. Reply Brief Under 37 C.F.R. s 41.37** Out Of Plan Ex Parte Martine Clozel. 2014 WL 12576231, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	Aug. 26, 2014	Administrative Filing		—
Cited by	**4. Examiner's Answer** Out Of Plan Ex Parte Martine Clozel. 2014 WL 12576230, *1+ , Patent Tr. & App. Bd. (Administrative Filing)	June 26, 2014	Administrative Filing		—
—	**5. PRODUCT, USEFUL TO TREAT E.G. HYPERTENSION AND HEART FAILURE, COMPRISES BROMO-PHENYL-BROMO-PYRIMIDINYLOXY-ETHOXY-PYRIMIDIN-YLAMINO-METHYL-PROPYL-AMINO SULFONYL AND COMPOUND HAVING PHOSPHODIESTERASE-5 INHIBITORY PROPERTIES** Out Of Plan DWPI 2008-J70674+	Aug. 29, 2006	DWPI	—	—
—	**6. COMBINATION COMPRISING MACITENTAN AND PACLITAXEL FOR TREATING MULTI-DRUG RESISTANT OVARIAN CANCER** Out Of Plan US PAT 8541433 , U.S. PTO Utility The invention relates to the combination of an endothelin receptor antagonist of formula (I) with paclitaxel, and in particular to this combination for therapeutic use,...	Sep. 24, 2013	Patents	—	—

Treatment	Title	Date	Type	Depth	Headnote(s)
—	**7. PROCESSES FOR PREPARING AMINE SALTS OF SILDENAFIL-ANALOGUES AND USE THEREOF** Out Of Plan US PAT 8497370 , U.S. PTO Utility A series of amine salts including a structure of formula (I) and formula (III) have provided. In formula I or formula (III), R 1, Ra and RX are as defined in the specification. The...	July 30, 2013	Patents	—	—
—	**8. RF 028787/0964** Out Of Plan	Aug. 15, 2012	Assignments	—	—
—	**9. THERAPEUTIC COMPOSITIONS** Out Of Plan US PAT APP 20130210830 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	Aug. 15, 2013	Patents	—	—
—	**10. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 9597331 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination with at least one compound...	Mar. 21, 2017	Patents	—	—
—	**11. STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING A PYRIMIDINE-SULFAMIDE** Out Of Plan US PAT 9265762 , U.S. PTO Utility The invention relates to stable pharmaceutical compositions comprising the compound of the below formula, or pharmaceutically acceptable salts, solvates, hydrates or morphological...	Feb. 23, 2016	Patents	—	—
—	**12. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 9173881 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination of at least one compound...	Nov. 03, 2015	Patents	—	—
—	**13. THERAPEUTIC COMPOSITIONS CONTAINING MACITENTAN** Out Of Plan US PAT 8809334 , U.S. PTO Utility The invention relates to a product containing the compound of formula (I) below or a pharmaceutically acceptable salt of this compound, in combination with at least one compound...	Aug. 19, 2014	Patents	—	—

Treatment	Title	Date	Type	Depth	Headnote(s)
—	**14. THERAPEUTIC COMPOSITIONS** Out of Plan US PAT APP 20140148460 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	May 29, 2014	Patents	—	—
—	**15. THERAPEUTIC COMPOSITIONS** Out of Plan US PAT APP 20130005734 , U.S. PTO Application The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one...	Jan. 03, 2013	Patents	—	—

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
96/000,237	09/22/2017	8268847		5019

45511 7590 02/08/2018

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
KUGEL, TIMOTHY J	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
02/08/2018	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of Intent to Issue Ex Parte Reexamination Certificate	Control No.	Patent Under Reexamination	
	96/000,237	8268847	
	Examiner	Art Unit	AIA (First Inventor to File) Status
	Timothy J. Kugel	3991	No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ Prosecution on the merits is (or remains) closed in this *ex parte* reexamination proceeding. This proceeding is subject to reopening at the initiative of the Office or upon petition. *Cf.* 37 CFR 1.313(a). A Certificate will be issued in view of
   (a) ☒ Patent owner's communication(s) filed: *16 January 2018*.
   (b) ☐ Patent owner's failure to file an appropriate timely response to the Office action mailed: _____.
   (c) ☐ Patent owner's failure to timely file an Appeal Brief (37 CFR 41.31).
   (d) ☐ The decision on appeal by the ☐ Board of Patent Appeals and Interferences ☐ Court dated _____
   (e) ☐ Other: _____.
2. The Reexamination Certificate will indicate the following:
   (a) Change in the Specification: ☐ Yes ☒ No
   (b) Change in the Drawing(s): ☐ Yes ☒ No
   (c) Status of the Claim(s):
      (1) Patent claim(s) confirmed: *1-11*.
      (2) Patent claim(s) amended (including dependent on amended claim(s)): _____
      (3) Patent claim(s) canceled: _____.
      (4) Newly presented claim(s) patentable: 12-57.
      (5) Newly presented canceled claims: _____.
      (6) Patent claim(s) ☐ previously ☐ currently disclaimed: _____
      (7) Patent claim(s) not subject to reexamination: _____.
3. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
4. ☒ Note the attached statement of reasons for patentability and/or confirmation. Any comments considered necessary by patent owner regarding reasons for patentability and/or confirmation must be submitted promptly to avoid processing delays. Such submission(s) should be labeled: "Comments On Statement of Reasons for Patentability and/or Confirmation."
5. ☐ Note attached NOTICE OF REFERENCES CITED (PTO-892).
6. ☐ Note attached LIST OF REFERENCES CITED (PTO/SB/08 or PTO/SB/08 substitute).
7. ☐ The drawing correction request filed on _____ is: ☐ approved ☐ disapproved.
8. ☒ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☒ All b)☐ Some* c)☐ None of the certified copies have
   ☐ been received.
   ☐ not been received.
   ☒ been filed in Application No. *12/439,290*.
   ☐ been filed in reexamination Control No. _____.
   ☐ been received by the International Bureau in PCT Application No. _____.

   * Certified copies not received: _____.
9. ☐ Note attached Examiner's Amendment.
10. ☐ Note attached Interview Summary (PTO-474).
11. ☐ Other: _____.

All correspondence relating to this reexamination proceeding should be directed to the **Central Reexamination Unit** at the mail, FAX, or hand-carry addresses given at the end of this Office action.

/Timothy J. Kugel/ and /Kendra Carter/ Patent Reexamination Specialists, CRU 3991	/Jean Witz/ Supervisory Patent Reexamination Specialist, CRU 3991

cc: Requester (if third party requester)

Reexamination Action

This is an *Ex Parte* Notice of Intent to Issue a Reexam Certificate in Reexamination Proceeding 96/000237.

Since the patent under reexamination has an effective filing date prior to 16 March 2013, this reexamination proceeding is taking place under the pre-AIA first to invent provisions. The text of those sections of Title 35, US Code not included in this action can be found in a prior Office action.

Status of the Proceeding

On 22 September 2017	A Request for Supplemental Examination of **claims 1-11** of US Patent 8,268,847 (the '847 patent) was filed by Patent Owner.
On 26 September 2017	A Notice of Supplemental Examination Request Filing Date was mailed.
On 25 October 2017:	A Supplemental Examination Certificate, noting that a substantial new question of patentability affecting at least one claim of the '847 patent was raised in the request for supplemental examination, was mailed.
On 13 November 2017:	An Order, ordering *ex parte* reexamination of **claims 1-11** of US Patent 8,268,847, and a first action on the merits non-final rejection were mailed.
On 27 December 2017:	An Examiner Interview Summary, detailing the interview conducted on 20 December 2017 was mailed.
On 16 January 2018:	Patent owner filed an amendment, which is herein entered and fully considered.

Status of the claims:

Claims 1-11 were issued in US Patent 8,268,847

No claims have been amended.

Claims 12-57 have been added.

Claims 1-57 are subject to this reexamination.

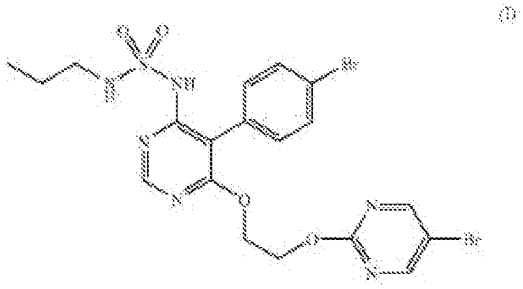
Claims 1-11 are confirmed.

Newly presented **claims 12-57** are patentable.

Claim Scope and Interpretation

In reexamination, patent claims are construed broadly. *In re Yamamoto*, 740 F2nd 1569, 1571 222 USPQ 934,936 (Fed Cir 1984) claims are given "their broadest reasonable interpretation consistent with the specification".

The '847 patent contains **claims 1-57** directed to a product of FORMULA (I) and at least one compound having PDE5 inhibitory properties. Sole independent **claim 1** is representative:

> 1. A product containing the compound of Formula (I) below
>
> 
>
> in free or pharmaceutically acceptable salt form, in combination with at least one compound having PDE5-inhibitory properties, in free or a pharmaceutically acceptable salt form, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

References Cited

The following references are cited in this Office action:

- US Patent 7,094,781 issued to Bolli *et al.* on 22 August 2006, hereinafter BOLLI '781[1].
- US Patent 8,367,685 issued to Adesuyi *et al.* on 05 February 2013, hereinafter ADESUYI[2].
- International Application Publication WO 02/053557 by Bolli *et al.*, published on 11 July 2002, hereinafter BOLLI '557[1].
- International Application Publication WO 2006/026395 by Keyser *et al.*, published on 09 March 2006, hereinafter KEYSER[1].

Response to Arguments

Patent owner persuasively argues (Response filed 16 January 2018, pp. 8-12) that the Patent Trial and Appeal Board (PTAB) found in Application 13/604148 (Patent Board Decision mailed 03 October 2016, pp. 3 and 8-10) that "…the administration of the compound of formula (I) and a PDE5 antagonist decreased blood pressure in an amount much greater than either compound alone, thus producing a synergistic effect"; that "…an ordinarily skilled artisan would not have expected the synergistic effects…"; and that "…the skilled artisan most likely would have expected inferior results based on the discussion in Keyser."

Adopting the reasoning of the PTAB, since one of ordinary skill in the art at the time the invention was made would not have considered modifying the disclosures of

[1] BOLLI '781, BOLLI '557, and KEYSER each qualifies as prior art under pre-AIA 35 USC §102(b).
[2] ADESUYI does not qualify as prior art under pre-AIA 35 USC §102, but raises the issue of non-statutory double patenting.

either BOLLI reference or ADESUYI with the teachings of KEYSER, the following have been withdrawn:

The rejection of claims 1-11 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 9 of BOLLI '781 in view of KEYSER has been withdrawn.

The rejection of claims 1-11 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of ADESUYI, as evidenced by BOLLI '557, in view of KEYSER has been withdrawn.

The rejection of claims 1-11 as being unpatentable under pre-AIA 35 USC §103(a) as being obvious over KEYSER in view of BOLLI '781 has been withdrawn.

The rejection of claims 1-11 as being unpatentable under 35 USC §103(a) as being obvious over KEYSER in view of BOLLI '557 has been withdrawn.

Allowable Subject Matter

1. **Claims 1-11 are confirmed and newly presented claims 12-57 are patentable**.

The following is an examiner's statement of reasons for confirmation and patentability:

KEYSER, BOLLI '781 and BOLLI '557 are the closest prior art made of record.

The BOLLI references disclose the compound of formula (I), but fail to teach or fairly suggest its use in combination with a PDE5 inhibitor. KEYSER discloses the use of PDE5 inhibitors, but the PTAB has found that one of ordinary skill in the art would not

have expected that, given the disclosure of KEYSER, the synergistic effect described in the disclosure of the patent under reexamination, and "…most likely would have expected inferior results…" in the use of the claimed combination.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

/Timothy J. Kugel/
Patent Reexamination Specialist, CRU 3991

Conferees:

/Kendra D. Carter/
Patent Reexamination Specialist (Detailee), CRU 3991

/Jean C. Witz/
Supervisory Patent Reexamination Specialist, CRU 3991

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000237	8268847
	Examiner	**Art Unit**
	TIMOTHY J KUGEL	3991

CPC								
Symbol							**Type**	**Version**
A61K		31	/	513			F	2013-01-01
A61K		31	/	4985			I	2013-01-01
A61K		31	/	506			I	2013-01-01
A61K		31	/	519			I	2013-01-01
A61K		31	/	53			I	2013-01-01
A61K		45	/	06			I	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	4985	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	506	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	519	I	3	1	2013-01-01
A61K		2300	/	00	A	3	2	2013-01-01
A61K		31	/	53	I	4	1	2013-01-01
A61K		2300	/	00	A	4	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	57	
/TIMOTHY J KUGEL/ Primary Examiner, Art Unit 3991	01/24/2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No. 20180123

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000237	8268847
	Examiner	**Art Unit**
	TIMOTHY J KUGEL	3991

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	269

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
546	274.4				

INTERNATIONAL CLASSIFICATION										
CLAIMED					**NON-CLAIMED**					
A	0	1	N	43 / 54 (2006.0)						
A	6	1	K	31 / 505 (2006.0)						
C	0	7	D	401 / 00 (2006.0)						

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	57	
/TIMOTHY J KUGEL/ Primary Examiner, Art Unit 3991	01/24/2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000237	8268847
	Examiner	**Art Unit**
	TIMOTHY J KUGEL	3991

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	17	33	33	49	49								
2	2	18	18	34	34	50	50								
3	3	19	19	35	35	51	51								
4	4	20	20	36	36	52	52								
5	5	21	21	37	37	53	53								
6	6	22	22	38	38	54	54								
7	7	23	23	39	39	55	55								
8	8	24	24	40	40	56	56								
9	9	25	25	41	41	57	57								
10	10	26	26	42	42										
11	11	27	27	43	43										
12	12	28	28	44	44										
13	13	29	29	45	45										
14	14	30	30	46	46										
15	15	31	31	47	47										
16	16	32	32	48	48										

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	57	
/TIMOTHY J KUGEL/ Primary Examiner, Art Unit 3991	01/24/2018	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office Part of Paper No. 20180123

Reexamination	Application/Control No. 96000237	Applicant(s)/Patent Under Reexamination 8268847
	Certificate Date	Certificate Number C1

Requester Correspondence Address: ☒ Patent Owner ☐ Third Party

LITIGATION REVIEW ☒	TJK (examiner initials)	01/25/2018 (date)
Case Name		Director Initials
None		jcw for jc

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	NUMBER
1. None	

UNITED THERAPEUTICS CORP., EX1003, page 381
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Bibliographic Data

Application No: 96000237

Foreign Priority claimed: (•) Yes ( ) No

35 USC 119 (a-d) conditions met: [✓] Yes [ ] No [ ] Met After Allowance

Verified and Acknowledged: /Timothy J. Kugel/ Examiner's Signature | Initials

Title: THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/22/2017	514	3991	
RULE			

APPLICANTS

INVENTORS

8268847,

ACTELION PHARMACEUTICALS, LTD., ALLSCHWIL, SWITZERLAND

PATENT OWNER,

CONTINUING DATA

This application is a SER of 12439290 02/27/2009 PAT 8268847

12439290 is a 371 of PCT/IB07/53448 08/28/2007

FOREIGN APPLICATIONS

PCT/IB2006/052999 08/29/2006

PCT/IB2006/053857 10/19/2006

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UNITED STATES

FILING FEE RECEIVED

$16,500

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*	*Complete if Known*	
	Application Number	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
	Examiner Name	Kugel, Timothy J
	Attorney Docket Number	103693.000585

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document
	1	2005/0101608	05-12-2005	Santel
	2	2010/0004274	01-07-2010	Adesuyi et al.
	3	2011/0136818	06-09-2011	Clozel
	4	2013/0005734	01-03-2013	Clozel
	5	2013/0190336	07-25-2013	Adesuyi et al.
	6	2013/0310407	11-21-2013	Regenass et al.
	7	2013/0317048	11-28-2013	Clozel et al.
	8	2014/0148460	05-29-2014	Clozel
	9	2014/0329824	11-06-2014	Clozel
	10	6,458,805	10-01-2002	Blok et al.
	11	8,541,433	09-24-2013	Clozel et al.
	12	8,809,334	08-19-2014	Clozel
	13	9,173,881	11-03-2015	Clozel

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number -Kind Code (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T*
	14	JP 2005-504113	02-10-2005	Novartis Pharma GMBH		T
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Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*	*Complete if Known*	
	Application Number	96/000,237
	Filing Date	September 22, 2017
	First Named Inventor	8,268,847
	Art Unit	3991
	Examiner Name	Kugel, Timothy J
	Attorney Docket Number	103693.000585

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T*
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Examiner Signature	/Timothy J. Kugel/	**Date Considered**	01/23/2018

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EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S13	6089	(A61K31/513).cpc. 514/269.ccls.	US-PGPUB; USPAT	OR	OFF	2018/01/23 07:33
S14	2991	S13 and @pd<"20100101"	US-PGPUB; USPAT	OR	ON	2018/01/23 07:35
S15	3098	S13 not S14	US-PGPUB; USPAT	OR	ON	2018/01/23 07:35

1/23/2018 7:52:59 AM
C:\Users\tkugel\Documents\1Active\96000237\96000237.wsp

UNITED THERAPEUTICS CORP., EX1003, page 386
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	96000237	8268847
	Examiner	Art Unit
	TIMOTHY J KUGEL	3991

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

SEARCH NOTES		
Search Notes	Date	Examiner
Reviewed litigation search performed on 20170925 - No litigation found	20171010	TJK
Reviewed prosecution history, file wrapper and references cited in parent application 12/439290	20170110	TJK
Reviewed references cited on IDS filed 20180122	20180123	TJK
Reviewed updated litigation search performed on 20180125 - No litigation found	20180125	TJK

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K31/513		20180123	TJK

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UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

US008268847C1

(12) EX PARTE REEXAMINATION CERTIFICATE (116th)

Ex Parte Reexamination Ordered under 35 U.S.C. 257

United States Patent

Clozel

(10) Number: US 8,268,847 C1
(45) Certificate Issued: Apr. 16, 2018

(54) **THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR**

(75) Inventor: **Martine Clozel**, Binningen (CH)

(73) Assignee: **ACTELION PHARMACEUTICALS LTD.**, Allschwil (CH)

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§ 371 (c)(1),	
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A61K 31/513	(2006.01)
A61K 31/4985	(2006.01)
A61K 31/506	(2006.01)
A61K 31/519	(2006.01)
A61K 31/53	(2006.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/513*** (2013.01); ***A61K 31/4985*** (2013.01); ***A61K 31/506*** (2013.01); ***A61K 31/519*** (2013.01); ***A61K 31/53*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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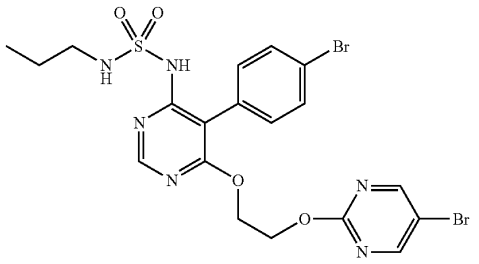
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Primary Examiner — Timothy J Kugel

(57) **ABSTRACT**

The invention relates to a product containing the compound of formula (I) below

(I)



or a pharmaceutically acceptable salt of this compound, in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

EX PARTE REEXAMINATION CERTIFICATE

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1-11** is confirmed.

New claims **12-57** are added and determined to be patentable.

12. The method of claim 11, wherein the compound having PDE5-inhibitory properties is tadalafil.

13. The method of claim 11, wherein the compound having PDE5 inhibitory properties is sildenafil.

14. The method of claim 12, wherein the method is for the treatment of pulmonary hypertension.

15. The method of claim 14, wherein the pulmonary hypertension is pulmonary arterial hypertension.

16. The method of claim 13, wherein the method is for the treatment of pulmonary hypertension.

17. The method of claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

18. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered simultaneously.

19. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered separately.

20. The method of claim 15, wherein the compound of formula (I) and tadalafil are administered over a period of time.

21. The method of claim 20, wherein the interval between the administration of the compound of formula (I) and the administration of tadalafil does not exceed two days.

22. The method of claim 21, wherein the interval does not exceed one day.

23. The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

24. The method of claim 23, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

25. The method of claim 15, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

26. The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

27. The method of claim 26, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

28. The method of claim 18, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

29. The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

30. The method of claim 29, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

31. The method of claim 20, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

32. The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

33. The method of claim 32, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

34. The method of claim 21, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

35. The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

36. The method of claim 35, wherein tadalafil is administered in a dose of 0.01 mg to 1 mg per kilogram of patient body weight.

37. The method of claim 22, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

38. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered simultaneously.

39. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered separately.

40. The method of claim 17, wherein the compound of formula (I) and sildenafil are administered over a period of time.

41. The method of claim 40, wherein the interval between the administration of the compound of formula (I) and the administration of sildenafil does not exceed two days.

42. The method of claim 41, wherein the interval does not exceed one day.

43. The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

44. The method of claim 43, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

45. The method of claim 17, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

46. The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

47. The method of claim 46, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

48. The method of claim 38, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

49. The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

50. The method of claim 49, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

51. The method of claim 40, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

52. The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

53. The method of claim 52 wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

54. The method of claim 41, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

55. The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.05 mg to 2 mg per kilogram of patient body weight.

56. The method of claim 55, wherein sildenafil is administered in a dose of 0.1 mg to 2 mg per kilogram of patient body weight.

57. The method of claim 42, wherein the compound of formula (I) is administered in a dose of 0.1 mg to 1 mg per kilogram of patient body weight.

* * * * *