PTO/SB/05 (08-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	AC-66-USC
First Inventor	Martine CLOZEL
Title	Therapeutic Compositions...
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria VA 22313-1450

1. [✓] **Fee Transmittal Form** (e.g., PTO/SB/17)
2. [ ] **Applicant claims small entity status.** See 37 CFR 1.27
3. [✓] **Specification** [*Total Pages* 13]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. [ ] **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets*]
5. **Oath or Declaration** [*Total Sheets*]
   a. [ ] Newly executed (original or copy)
   b. [✓] A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. [ ] DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [✓] **Application Data Sheet.** See 37 CFR 1.76
7. [ ] **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   [ ] 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 or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. [✓] **Assignment Papers** (cover sheet & document(s))
   Name of Assignee ACTELION PHARMACEUTICALS LTD.
10. [ ] **37 CFR 3.73(b) Statement** *(when there is an assignee)* [✓] **Power of Attorney**
11. [ ] **English Translation Document** *(if applicable)*
12. [✓] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
13. [✓] **Preliminary Amendment**
14. [ ] **Return Receipt Postcard** (MPEP 503)
    (Should be specifically itemized)
15. [ ] **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. [ ] **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. [ ] Other:

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

[✓] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: 12/439,290

Prior application information: *Examiner* Kendra CARTER *Art Unit:* 1627

19. CORRESPONDENCE ADDRESS

[✓] The address associated with Customer Number: 50446 *OR* [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature		Date	Sept 5 2012
Name (Print/Type)	Brittany L.A	Registration No. (Attorney/Agent)	58,337

This collection of information is required by 37 CFR 1.53(b). 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AC-66-USC
	Application Number	
Title of Invention	THERAPEUTIC COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Martine		CLOZEL	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Binnigen	Country Of Residence	CH
Citizenship under 37 CFR 1.41(b)	FR		

Mailing Address of Applicant:

Address 1	Winterhalde 3b		
Address 2			
City	Binnigen	State/Province	
Postal Code	CH-4102	Country	CH

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	50446		
Email Address	file@hoxpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	THERAPEUTIC COMPOSITIONS		
Attorney Docket Number	AC-66-USC	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AC-66-USC
	Application Number	
Title of Invention	THERAPEUTIC COMPOSITIONS	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	50446		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	12439290	2009-02-27
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12439290	a 371 of international	PCT/IB2007/053448	2007-08-28
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/IB2007/053448	non provisional of	PCT/IB2006/052999	2006-08-29
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/IB2007/053448	non provisional of	PCT/IB2006/053857	2006-10-19

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AC-66-USC
	Application Number	
Title of Invention	THERAPEUTIC COMPOSITIONS	

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	Actelion Pharmaceuticals Ltd		
Mailing Address Information:			
Address 1	Gewerbestrasse 16		
Address 2			
City	Allschwil	**State/Province**	
Country	CH	Postal Code	CH-4123
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature				Date (YYYY-MM-DD)	2013-04-05
First Name	Brittany	Last Name	LA	Registration Number	58337

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

Attorney Docket No. AC-66-USC

(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine Clozel	)	Confirmation No.: TBD
Serial No.:	TBD	)	Group Art Unit: TBD
Filed:	September 5, 2012	)	Examiner: TBD
Title:	THERAPEUTIC COMPOSITIONS	)	Docket No.: AC-66-USC

PRELIMINARY AMENDMENT

Mail Stop Patent Application
Commissioner for Patents
P.O.Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Prior to examination of the above-captioned application (filed herewith), please enter the amendments to the claims as set forth herein.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Specification

Please amend the paragraph following the title on page 1:

Cross Reference to Related Applications

This application is a continuation of U.S. Appl. No. 12/439,290, filed on February 27, 2009, which is a United States National Stage Application under 35 U.S.C. 371 of PCT Application No. PCT/IB2007/053448, filed on August 28, 2007, which claims the benefit of PCT Application No. PCT/IB2006/052999, filed on August 29, 2006, and PCT Application No. PCT/IB2006/053857, filed on October 19, 2006, the contents of each of which are incorporated herein by reference in their entirety.

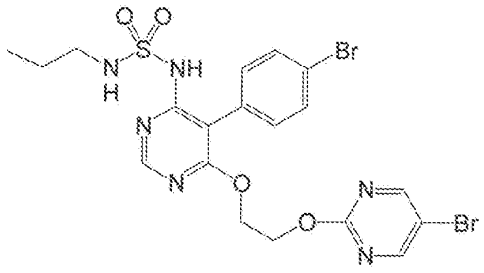
UNITED THERAPEUTICS CORP., EX1006, page 6
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. The method according to claim 4, wherein the administration of the compound of formula

UNITED THERAPEUTICS CORP., EX1006, page 7
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

(I) will be alternated with the administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

6. The method according to claim 5, wherein said administration will not exceed one day.

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

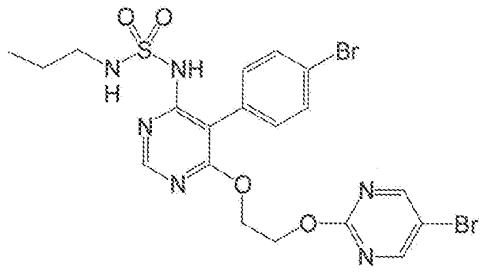
8. The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

9. The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

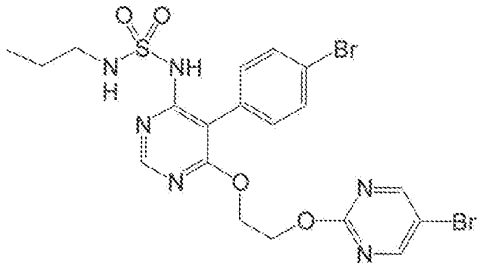


(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 8
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

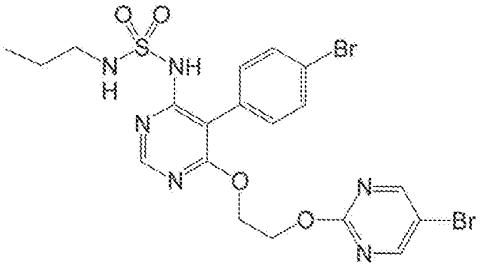
13. A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 9
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

REMARKS/ARGUMENTS

The specification has been amended to update the section on related applications.

Claims 1-14 have replaced original claims 1-12. Support for the claims may be found as follows:

Claim 1 – page 1, lines 1-6 (also page 6, lines 1-8); page 5, lines 22 and 26-27.

Claim 2 - page 4, lines 10-12.

Claim 3 – page 1, line 5.

Claim 4 – page 4, lines 13-15.

Claim 5 – page 4, lines 19-21.

Claim 6 – page 4, lines 19-22.

Claim 7 – page 5, lines 1-3.

Claim 8 – page 5, lines 4-5.

Claim 9 – page 5, lines 6-7.

Claim 10 – page 5, lines 25-26.

Claim 11 – page 5, lines 25-27.

Claim 12 – page 5, lines 4-7; page 4, lines 10-12.

Claim 13 – page 5, lines 4-7; page 4, lines 13-15.

Claim 14 – page 5, lines 4-17; page 1, line 5.

It is believed no new matter has been added.

Pursuant to 35 U.S.C. § 41 and 37 C.F.R. § 1.16, the filing fee, search fee, and examination fee are submitted herewith. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), please charge the same to Deposit Account 50-4255.

Applicant earnestly solicits early examination and allowance of these claims. In the event there are any questions, please do not hesitate to contact the undersigned by telephone.

UNITED THERAPEUTICS CORP., EX1006, page 10
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Respectfully Submitted,

Date Sept 5, 2012

By

Brittany La
Reg. No. 58,337
Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, NJ 07041
(973) 912-5232

UNITED THERAPEUTICS CORP., EX1006, page 11
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	TBD
Serial No.:	TBD	Group Art Unit:	TBD
Filed:	September 5, 2012	Confirmation No.:	TBD
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq.*, the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicant respectfully requests that this Information Disclosure Statement be entered and the documents listed on the attached form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

The filing of this Information Disclosure Statement is not be be construed as a representation that a search has been made, nor construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability or prior art.

Pursuant to 37 C.F.R. §1.98(d), copies of the listed documents are not provided as these references were previously cited by or submitted to the U.S. Patent Office in connection with Applicant's prior U.S. application, Serial No. 12/439,290, filed on February 27, 2009, which is relied upon for an earlier filing date under 35 U.S.C. §120.

Pursuant to 37 C.F.R. §1.97(b), it is believed that no fee or statement is required with the Information Disclosure Statement. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), please charge the same to Deposit Account 50-4255. If there are any questions relating to fee payments associated with this application, please contact the undersigned attorney at the contact information listed below.

Respectfully submitted,

Date Sept 5, 2012 By _____

Brittany LA
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, New Jersey 07041
973-912-5232
973-912-5236 (fax)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 1 of 3	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate
		US 4,233,294	11/11/1980	Maurer, et al.	
		US 5,250,534	10/05/1993	Bell, et al.	
		US 5,292,740	03/08/1994	Burri, et al.	
		US 5,859,006	01/12/1999	Daugan, et al.	
		US 7,094,781	08/22/2006	Bolli, et al.	
		US 7,285,549	10/23/2007	Bolli, et al.	
		US 2008/0233188	09/25/2008	Adesuyi, et al.	
		US 2010/0022568	01/28/2010	Clozel, et al.	
		US 2010/0004274	01/07/2010	Adesuyi, et al.	

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		AU 678467 B2	05/29/1997	F. Hoffmann-La Roche AG	
		EP 0743307	11/20/1996	Yamada, et al.	
		EP 0657548	06/21/1995	Yamada, et al.	
		EP 0882719	12/09/1998	Harada, et al.	
		EP 0959072	11/24/1999	TANABE SEIYAKU CO [JP]	
		EP 1097711	05/09/2001		
		WO 96/016963	06/06/1996	F. HOFFMAN–LA ROCHE AG	
		WO 96/019459	06/27/1996	F. HOFFMAN–LA ROCHE AG	
		WO 00/042035	07/20/2000	F. HOFFMAN–LA ROCHE AG	
		WO 01/017976	06/15/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/046156	06/28/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/081335	11/01/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/081338	11/01/2001	01/081338	
		WO 02/053557	07/11/2002		
		WO 99/024433	05/20/1999		
		WO 00/027848	05/18/2000		

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 2 of 3	Attorney Docket No:	AC-66-USC

		WO 2007/031933	03/22/2007		
		WO 2006/026395	03/09/2006		
		WO 1999/064004	12/16/1999		

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
		NEIDHART, W., et al. "Discovery of RO 48-5695: A Potent Mixed Endothelin Receptor Optimized from Bosentan", Bioorganic & Medical Chemistry Letters, Vol. 7, No. 17, pp. 2223-2228, 1997.	
		GOHRING, W., et al., "Development of a Process to Prepare 2-Cyanopyrimidine on Commercial Scale", Chimia, Vol. 50, pp. 538-543, November 1996.	
		NUGENT, R., et al., "Pyrimidine Thioethers: A Novel Class of HIV-1 Reverse Transcriptase Inhibitors with Ativity Against BHAP-Resistant HIV", J. Med. Chem., Vol. 41, pp. 3793-3803, 1998.	
		MARCH, J., "Advanced Organic Chemistry (Fourth Edition)", p. 449 and references cited therein, 1992.	
		KOHARA, Y., et al., "Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres, J. Med. Chem. Vol. 39, pp. 5228-5235, 1996.	
		WEISS, G., et al., Liebigs Ann. Chem., Vol. 729, pp. 40-51, 1969.	
		KLOEK, J., et al., "An Improved Synthesis of Sulfamoyl Chlorides, J. Org. Chem., Vol. 41, No. 25, pp. 4028-4029, 1976.	
		DICKINSON, R., et al., "Thromboxane Modulating Agents. 3. IH-Imidazol-1-y[alkyl-and 3-Pyridinylalkyl-Substituted 3-[2-((Arylsulfonyl]amino)ethyl]benzenepropanoic Acid Derivatives as Dual Thromboxane Synthase Inhibitor/Thromboxane Receptor Antagonists", J. Med. Chem., Vol. 40, pp. 3442-3452, 1997.	
		COHEN, E., et al., "Sulfamoyl Chloride, Sulfamides and Sulfimide", J. Am. Chem. Soc., Vol. 84, pp. 1994-2002, 1962.	
		OLSON, R., et al., "Orally Active Isoxazoline Glycoprotein IIb/IIIa Antagonists with Extended Duration of Action", J. Med. Chem., Vol. 42, pp. 1178-1192, 1999.	
		CROSBY, D., et al., "n-Butyl 5-Chloro-2-pyrimidoxyacetate-A Plant Growth Regulator Analog", J.Org. Chem., Vol. 25, pp. 1916-1919, November 1960.	
		MORGAN, E.D., "Synthesis of p-ALkylphenylacetic Acid", Tetrahedron, Vol. 23, pp. 1735-1738, 1967.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 060310

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 3 of 3	Attorney Docket No:	AC-66-USC

		TOZER, M., et al., "4-Chlorobenzyl Sulfonamide and Sulfamide Derivatives of Histamine Homologues: The Design of Potent Histamine H3 Receptor Antagonists", Bioorganic & Medicinal Chemistry Letter Vol. 9, pp. 3103-3108, 1999.	
		DEWYNTER, G., et al., Tetrahedron, Vol. 49, No. 1, pp. 65-76, 1993.	
		BENNETT, J. Claude, et al., Textbook of Medicine Vol. 1, 20th Edition, pp. 1004-1010 (1996).	
		RUBANYI, G.M., et al., Endothelins: Molecular Biology, Biochemistry, Pharmacology, Physiology and Pathophysiology, Pharm. Reviews, Vol. 46, No. 3, 1994.	
		ARAI, H., et al., "Cloning & Expression of a cDNA Encoding an Endothelin Receptor", Nature, Vol. 348, pp. 730-732, 1990.	
		BREU, V., et al. "In vitro Characterization of Ro 48-2005, a Novel Synthetic Non-Peptide Endothelin Antagonist of Eta and ETb Receptors", FEBS 13244, Vol. 334, No. 2, pp. 210-214, November 1993.	
		NEIDHART, W., et al., "The Discovery of Nonpeptide Endothelin Receptor Antagonists. Progression Towards Bosentan", Chimia, Vol. 50, pp. 519-524, November 1996.	
		McMILLEN, M., et al., "Endothelins: Polyfunctional Cytokines" J. Amer. College of Surgeons, Vol. 180, pp. 621-640.	
		OGAWA, Y., et al., "Molecular Cloning of a Non-Isopeptide-Selective Human Endothelin Receptor", Biochem. Biophy. Research Comm. VOl. 178, No. 1, pp. 248-255, July 1991.	
		OHLSTEIN, E., et al., "Endothelin-1 Modulates Vascular Smooth Muscle Structure and Vasomotion; Implications in Cardiovascular Pathology" Drug Development Research, Vol. 29, pp. 108-128, 1993.	
		SAKURAI, T., et al., "Cloning of cDNA Encoding a Non-Isopeptide-Selective Subtype of the Endothelin Receptor" Nature, Vol. 348, pp. 732-735, December 1990.	
		SUMNER, M., et al., "Endothelin Eta and ETb Receptors Mediate Vascular Smooth Muscle Contraction", Br.J. Pharmacol., Vol. 107, pp. 858-860, 1992.	
		YANAGISAWA, M., et al., "A Novel Potent Vasoconstrictor Peptide Produced by Vascular Endothelial Cells", Nature, Vol. 332, pp. 411-415, March 1988.	
		IGLARZ, M., et al., "Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 327, No. 3, pp. 736-745, (2008).	
		GOULD, P. L., "Salt Selection for Basic Drugs", International Journal of Pharmaceutics, (1986), Vol. 33, pp. 201-217.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

PTO/SB/17 (03-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

FEE TRANSMITTAL

Complete if known	
Application Number	TBD
Filing Date	Herewith
First Named Inventor	Martine CLOZEL
Examiner Name	Kendra CARTER
Art Unit	1627
Practitioner Docket No.	AC-66-USC

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,500.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☑ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 50-4255 Deposit Account Name: Hoxie & Associates LLC

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

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	380	190	620	310	250	125	1,250.00
Design	250	125	120	60	160	80	
Plant	250	125	380	190	200	100	
Reissue	380	190	620	310	750	375	
Provisional	250	125	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	60	30
Each independent claim over 3 (including Reissues)	250	125
Multiple dependent claims	450	225

Total Claims		Extra Claims	Fee ($)		Fee Paid ($)
14	-20 or HP =	0 x	80.00	=	0.00

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)		Fee Paid ($)
4	-3 or HP =	1 x	250.00	=	250.00

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 $310 ($155 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).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
13	- 100 =	0	/ 50 =	0 (round up to a whole number)	x	310.00	=	0.00

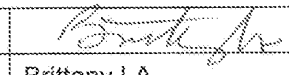
4. OTHER FEE(S) **Fees Paid ($)**

Non-English specification, $130 fee (no small entity discount)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small entity)

Other (e.g., late filing surcharge): _____

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 58,337	Telephone (973)912-5232
Name (Print/Type)	Brittany LA		Date Sept 5, 2012

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 March 2008 (06.03.2008)

PCT

(10) International Publication Number
WO 2008/026156 A2

(51) International Patent Classification:
A61K 31/4985 (2006.01) *A61K 31/53* (2006.01)
A61K 31/506 (2006.01) *A61K 45/06* (2006.01)
A61K 31/519 (2006.01) *A61P 9/00* (2006.01)

(21) International Application Number:
PCT/IB2007/053448

(22) International Filing Date: 28 August 2007 (28.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB2006/052999
29 August 2006 (29.08.2006) IB
PCT/IB2006/053857
19 October 2006 (19.10.2006) IB

(71) Applicant *(for all designated States except US)*: **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **CLOZEL, Martine** [FR/CH]; Winterhalde 3b, CH-4102 Binningen (CH).

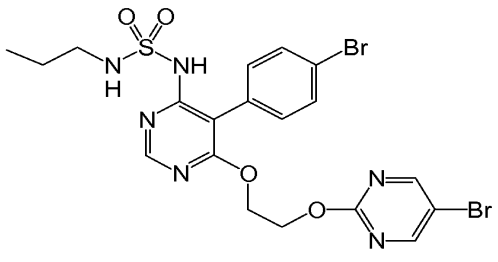
(74) Agent: **RUHLMANN, Eric**; c/o Actelion Pharmaceuticals Ltd, Legal Department, Gewerbestrasse 16, CH-4123 Allschwil (CH).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) **Title:** THERAPEUTIC COMPOSITIONS



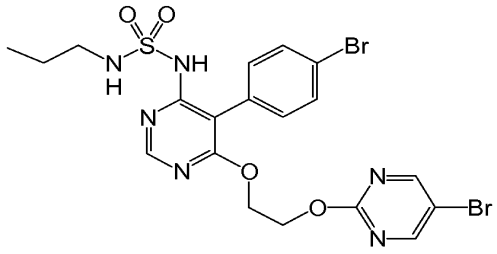
(I)

(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.

WO 2008/026156 A2

THERAPEUTIC COMPOSITIONS

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:

- US 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 1 097 711 (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);
- US 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.

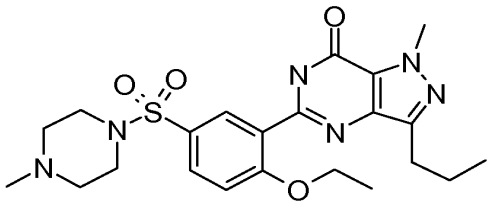
"Separately" or "separate", when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

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.

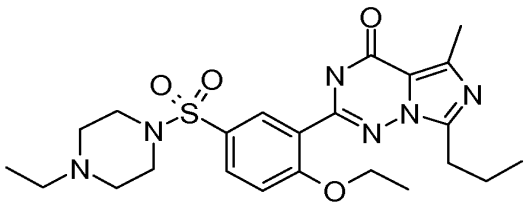
By "disease wherein vasoconstriction is involved" is meant in particular hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.

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.

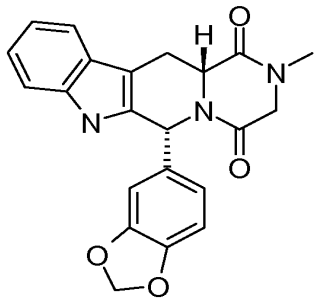
Specific examples of compounds having PDE5-inhibitory properties include the compounds having the following structures (names):



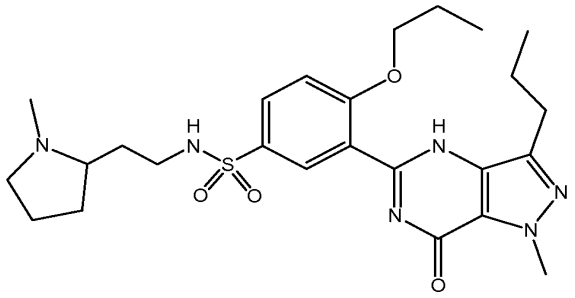
(sildenafil)



(vardenafil)



(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.

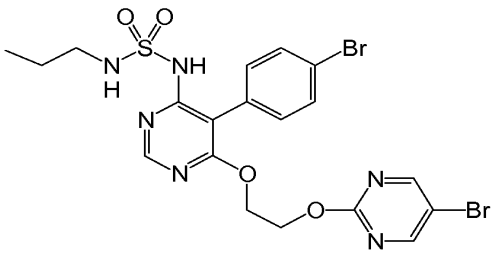
According to another particularly preferred variant of the invention the compound having PDE5-inhibitory properties will be tadalafil.

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).

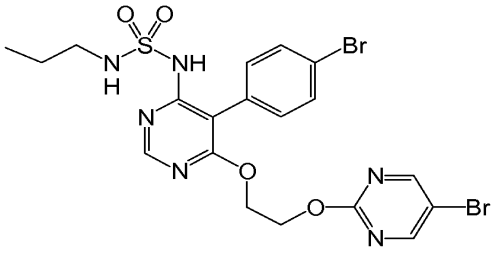
The invention also relates to a pharmaceutical composition containing, as active principles, the compound of formula (I) below



(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, MN, 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 xg) 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 PDE5inhibition 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, AG1-X2, 200-400 mesh) which has been already washed with 0.5*N* HCl, H_2O, 0.5*N* NaOH, H_2O, 0.5*N* HCl 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 administration 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

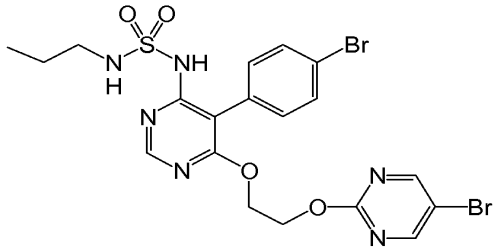
after oral gavage of the combination (compound of formula (I) at 0.3 mg/kg and tadalafil at 10 mg/kg) was 444, confirming the synergistic effect.

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.

Claims

1. 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.

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

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

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

5. A 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, or a pharmaceutically acceptable salt of said compound of formula (I), in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, as well as at least one excipient.

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

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

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

10. Use of the compound of formula (I) as described in claim 1, or a pharmaceutically acceptable salt of said compound of formula (I), in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament intended to treat a disease wherein vasoconstriction is involved.

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

12. Use according to claim 10, wherein the disease intended to be treated is selected from hypertension and pulmonary hypertension.

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney Docket No. AP-01

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter that is claimed and for which a patent is sought on the invention entitled

Title: THERAPEUTIC COMPOSITIONS COMPRISING A SPECIFIC ENDOTHELIN RECEPTOR ANTAGONIST AND A PDE5 INHIBITOR the specification of which (check one)

☐ is attached hereto and is identified as Attorney Docket #_____
☐ was filed in the United States on _____ as Application Serial No. _____
☒ was filed as PCT International Application No. PCT/IB2007/053448 on August 28, 2007.
☐ was deposited for filing under Attorney Docket No. _____ via Express Mail No. _____; Serial No. not yet known,

including all the amendments through the date hereof.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below:

PRIOR FOREIGN APPLICATIONS - PRIORITY CLAIMED			
NUMBER	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED (YES OR NO
PCT/IB2006/052999	IB	August 29, 2006	YES
PCT/IB2006/053857	IB	October 19, 2006	YES

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112. I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. PRIORITY		
APPLICATION SERIAL NO.	FILING DATE	STATUS-PATENTED, PENDING, ABANDONED

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney Docket No. AP-01

I hereby claim the benefit under Title 35, United States Code 119(e) of any United States provisional applications listed below.

US PROVISIONAL PRIORITY		
APPLICATION SERIAL NO.	FILING DATE	STATUS-PATENTED, PENDING, ABANDONED

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney Docket No. AP-01

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

All practitioners associated with Customer No. 50446

Send correspondence to:	**Direct Telephone Calls To:**
Thomas Hoxie (Reg. No. 32,993) Hoxie & Associates LLC 75 Main Street, Suite 301Millburn, NJ 07041 USA	Thomas Hoxie (Reg. No. 32,993) (973) 912-5232
FULL NAME OF SOLE OR FIRST INVENTOR CLOZEL, Martine	DATE 20 January 2009
INVENTOR'S SIGNATURE Martine Clozel	CITIZENSHIP French
RESIDENCE (City, State, Country) Binningen, Switzerland	
POST OFFICE ADDRESS (work or home) Winterhalde 3b, CH-4102 Binningen	

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Brittany La/Stephanie Owusu-Hemeng
Attorney Docket Number:	AC-66-USC
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Independent claims in excess of 3	1201	1	250	250
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1500

Electronic Acknowledgement Receipt	
EFS ID:	13664742
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La/Stephanie Owusu-Hemeng
Filer Authorized By:	Brittany La
Attorney Docket Number:	AC-66-USC
Receipt Date:	05-SEP-2012
Filing Date:	
Time Stamp:	16:25:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1500
RAM confirmation Number	3696
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		AC_66_USC_APP.pdf	6520637 85a2ad7dc96813cb9d08071cb355f530ad5137b9	yes	17

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Transmittal of New Application	1	1
Application Data Sheet	2	4
Preliminary Amendment	5	11
Transmittal Letter	12	13
Information Disclosure Statement (IDS) Form (SB08)	14	16
Fee Worksheet (SB06)	17	17

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

2		WO_2008026156.pdf	526291 45855b3b3d975b21cce703040e85d7abb47ca8d4	yes	13

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Abstract	1	1
Specification	2	11
Claims	12	13

Warnings:

Information:

3	Oath or Declaration filed	AC_66_USC_DECL.pdf	940415 0761ffcd08d4ec46cb7ab28d3382843349440a68	no	3

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	36226 e5dce0bf61116092eb8d6d644b319c49ee4e6e0b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	8023569	

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/604,148	09/05/2012	1629	1500	AC-66-USC	14	4

CONFIRMATION NO. 5499

50446
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

FILING RECEIPT

OC000000056752298

Date Mailed: 09/25/2012

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)
Martine CLOZEL, Binnigen, SWITZERLAND;

Applicant(s)
Martine CLOZEL, Binnigen, SWITZERLAND;

Assignment For Published Patent Application
Actelion Pharmaceuticals Ltd., Allschwil, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 50446

Domestic Priority data as claimed by applicant
This application is a CON of 12/439,290 02/27/2009 PAT 8268847
which is a 371 of PCT/IB2007/053448 08/28/2007

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/052999 08/29/2006
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2006/053857 10/19/2006

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 09/14/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/604,148**

Projected Publication Date: 01/03/2013

Non-Publication Request: No

Early Publication Request: No

Title

THERAPEUTIC COMPOSITIONS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

UNITED THERAPEUTICS CORP., EX1006, page 40
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage, facilitate, and accelerate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/604,148

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	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	14 minus 20 =	*			OR	x 60 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 250 =	250
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1500

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	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))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	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))							OR		
						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 found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC

CONFIRMATION NO. 5499

50446
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

PUBLICATION NOTICE

OC000000058446726

Title:THERAPEUTIC COMPOSITIONS

Publication No.US-2013-0005734-A1
Publication Date:01/03/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED THERAPEUTICS CORP., EX1006, page 43
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
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 01/09/2013

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
01/09/2013	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)	
	13/604,148	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 *05 September 2012*.

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) *1-14* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-14* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

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).

Priority under 35 U.S.C. § 119

12)☐ 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) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/12*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 are examined on the merits.

Information Disclosure Statement

The information disclosure statement filed September 5, 2012 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Particularly, the foreign documents EP 0743307 and EP 0657548, and the non-patent document Iglarz, M. et al. were not provided.

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 1-14 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 or sildenafil to treat pulmonary hypertension or pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not

exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be 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 combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

2) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 10 and 18 of copending Application No. 12/388,142 ('142) (recently allowed) 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 to treat pulmonary arterial hypertension.

The Application '142 does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary 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 combined to treat pulmonary hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or

three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

3) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent 8,268,847 ('847) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

The Patent '847 teaches a composition of formula I with a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary hypertension.

The Patent '847 does not teach the treatment of pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to treat pulmonary arterial hypertension with the combination because Keyser et al. teach that an ET antagonist

and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

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 1-14 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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Bolli et al. does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious and motivated 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 combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

To one skilled in the art it would be obvious and motivated to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

Conclusion

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 1 of 3	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS

Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate
		US 4,233,294	11/11/1980	Maurer, et al.	
		US 5,250,534	10/05/1993	Bell, et al.	
		US 5,292,740	03/08/1994	Burri, et al.	
		US 5,859,006	01/12/1999	Daugan, et al.	
		US 7,094,781	08/22/2006	Bolli, et al.	
		US 7,285,549	10/23/2007	Bolli, et al.	
		US 2008/0233188	09/25/2008	Adesuyi, et al.	
		US 2010/0022568	01/28/2010	Clozel, et al.	
		US 2010/0004274	01/07/2010	Adesuyi, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		AU 678467 B2	05/29/1997	F. Hoffmann-La Roche AG	
		~~EP 0743307~~	~~11/20/1996~~	~~Yamada, et al.~~	
		~~EP 0657548~~	~~06/21/1995~~	~~Yamada, et al.~~	
		EP 0882719	12/09/1998	Harada, et al.	
		EP 0959072	11/24/1999	TANABE SEIYAKU CO [JP]	
		EP 1097711	05/09/2001		
		WO 96/016963	06/06/1996	F. HOFFMAN–LA ROCHE AG	
		WO 96/019459	06/27/1996	F. HOFFMAN–LA ROCHE AG	
		WO 00/042035	07/20/2000	F. HOFFMAN–LA ROCHE AG	
		WO 01/017976	06/15/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/046156	06/28/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/081335	11/01/2001	ACTELION PHARMACEUTICALS LTD.	
		WO 01/081338	11/01/2001	01/081338	
		WO 02/053557	07/11/2002		
		WO 99/024433	05/20/1999		
		WO 00/027848	05/18/2000		

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 2 of 3	Attorney Docket No:	AC-66-USC

		WO 2007/031933	03/22/2007		
		WO 2006/026395	03/09/2006		
		WO 1999/064004	12/16/1999		

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
		NEIDHART, W., et al. "Discovery of RO 48-5695: A Potent Mixed Endothelin Receptor Optimized from Bosentan", Bioorganic & Medical Chemistry Letters, Vol. 7, No. 17, pp. 2223-2228, 1997.	
		GOHRING, W., et al., "Development of a Process to Prepare 2-Cyanopyrimidine on Commercial Scale", Chimia, Vol. 50, pp. 538-543, November 1996.	
		NUGENT, R., et al., "Pyrimidine Thioethers: A Novel Class of HIV-1 Reverse Transcriptase Inhibitors with Ativity Against BHAP-Resistant HIV", J. Med. Chem., Vol. 41, pp. 3793-3803, 1998.	
		MARCH, J., "Advanced Organic Chemistry (Fourth Edition)", p. 449 and references cited therein, 1992.	
		KOHARA, Y., et al., "Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres, J. Med. Chem. Vol. 39, pp. 5228-5235, 1996.	
		WEISS, G., et al., Liebigs Ann. Chem., Vol. 729, pp. 40-51, 1969.	
		KLOEK, J., et al., "An Improved Synthesis of Sulfamoyl Chlorides, J. Org. Chem., Vol. 41, No. 25, pp. 4028-4029, 1976.	
		DICKINSON, R., et al., "Thromboxane Modulating Agents. 3. IH-Imidazol-1-y[alkyl-and 3-Pyridinylalkyl-Substituted 3-[2-((Arylsulfonyl]amino)ethyl]benzenepropanoic Acid Derivatives as Dual Thromboxane Synthase Inhibitor/Thromboxane Receptor Antagonists", J. Med. Chem., Vol. 40, pp. 3442-3452, 1997.	
		COHEN, E., et al., "Sulfamoyl Chloride, Sulfamides and Sulfimide", J. Am. Chem. Soc., Vol. 84, pp. 1994-2002, 1962.	
		OLSON, R., et al., "Orally Active Isoxazoline Glycoprotein IIb/IIIa Antagonists with Extended Duration of Action", J. Med. Chem., Vol. 42, pp. 1178-1192, 1999.	
		CROSBY, D., et al., "n-Butyl 5-Chloro-2-pyrimidoxyacetate-A Plant Growth Regulator Analog", J.Org. Chem., Vol. 25, pp. 1916-1919, November 1960.	
		MORGAN, E.D., "Synthesis of p-ALkylphenylacetic Acid", Tetrahedron, Vol. 23, pp. 1735-1738, 1967.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 060310

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	TBD
	Filing Date:	HEREWITH
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 3 of 3	Attorney Docket No:	AC-66-USC

		TOZER, M., et al., "4-Chlorobenzyl Sulfonamide and Sulfamide Derivatives of Histamine Homologues: The Design of Potent Histamine H3 Receptor Antagonists", Bioorganic & Medicinal Chemistry Letter Vol. 9, pp. 3103-3108, 1999.	
		DEWYNTER, G., et al., Tetrahedron, Vol. 49, No. 1, pp. 65-76, 1993.	
		BENNETT, J. Claude, et al., Textbook of Medicine Vol. 1, 20th Edition, pp. 1004-1010 (1996).	
		RUBANYI, G.M., et al., Endothelins: Molecular Biology, Biochemistry, Pharmacology, Physiology and Pathophysiology, Pharm. Reviews, Vol. 46, No. 3, 1994.	
		ARAI, H., et al., "Cloning & Expression of a cDNA Encoding an Endothelin Receptor", Nature, Vol. 348, pp. 730-732, 1990.	
		BREU, V., et al. "In vitro Characterization of Ro 48-2005, a Novel Synthetic Non-Peptide Endothelin Antagonist of Eta and ETb Receptors", FEBS 13244, Vol. 334, No. 2, pp. 210-214, November 1993.	
		NEIDHART, W., et al., "The Discovery of Nonpeptide Endothelin Receptor Antagonists. Progression Towards Bosentan", Chimia, Vol. 50, pp. 519-524, November 1996.	
		McMILLEN, M., et al., "Endothelins: Polyfunctional Cytokines" J. Amer. College of Surgeons, Vol. 180, pp. 621-640.	
		OGAWA, Y., et al., "Molecular Cloning of a Non-Isopeptide-Selective Human Endothelin Receptor", Biochem. Biophy. Research Comm. VOl. 178, No. 1, pp. 248-255, July 1991.	
		OHLSTEIN, E., et al., "Endothelin-1 Modulates Vascular Smooth Muscle Structure and Vasomotion; Implications in Cardiovascular Pathology" Drug Development Research, Vol. 29, pp. 108-128, 1993.	
		SAKURAI, T., et al., "Cloning of cDNA Encoding a Non-Isopeptide-Selective Subtype of the Endothelin Receptor" Nature, Vol. 348, pp. 732-735, December 1990.	
		SUMNER, M., et al., "Endothelin Eta and ETb Receptors Mediate Vascular Smooth Muscle Contraction", Br.J. Pharmacol., Vol. 107, pp. 858-860, 1992.	
		YANAGISAWA, M., et al., "A Novel Potent Vasoconstrictor Peptide Produced by Vascular Endothelial Cells", Nature, Vol. 332, pp. 411-415, March 1988.	
		IGLARZ, M., et al., "Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 327, No. 3, pp. 736-745, (2008).	
		GOULD, P. L., "Salt Selection for Basic Drugs", International Journal of Pharmaceutics, (1986), Vol. 33, pp. 201-217.	

EXAMINER	/Kendra Carter/	DATE CONSIDERED	01/03/2013

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.C./

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	**Art Unit**
	KENDRA D CARTER	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/26/2012								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								

UNITED THERAPEUTICS CORP., EX1006, page 63
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	Art Unit
	KENDRA D CARTER	1627

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (eDAN,PALM)	12/6/12	KDC
STN	12/6/12	KDC
Google (macitentan, PDE5 inhibitor, hypertension, tadalafil, sildenafil)	12/6/12	KDC

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

UNITED THERAPEUTICS CORP., EX1006, page 64
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
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 01/17/2013

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
01/17/2013	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.** 13/604,148	**Applicant(s)** CLOZEL, MARTINE	
	Examiner KENDRA D. CARTER	**Art Unit** 1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KENDRA D. CARTER*. (3) *Brittany La*.

(2) *Sreeni Padmanabhan*. (4)_____.

Date of Interview: *09 January 2013*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-14*.

Identification of prior art discussed: *Bolli et al. and Keyser et al.*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The double patenting rejections and 35 U.S.C. 103 rejections were discussed. The Applicant will consider ODP rejections and filing TDs were appropriate. The Applicant argued that the Keyser reference wants more ETa selective compounds and that hidsight reconstruction was taken by the Examiner. The Applicant argued that one skilled in the art would not modify the compound 104 of Bolli et al. to the propyl when there are other compounds in the table that have higher ETa selectivity. The Examiner will consider the arguments in response to the recently issued Non-final rejection filed January 9, 2013 and suggested providing data between the the ethyl (compound 104) and propyl compounds (claimed compound)..

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 period 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.

☐ Attachment

/KENDRA D CARTER/ Examiner, Art Unit 1627	

UNITED THERAPEUTICS CORP., EX1006, page 66
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

REQUEST FOR CORRECTED PUBLICATION OF PATENT APPLICATION PURSUANT TO 37 C.F.R. § 1.221(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

The above-referenced application was published as U.S. Publication No. 2013/0005734. This publication, however, contains the following material errors:

In line 11 of Paragraph [0039], the "mM" is missing. The beginning of the line should read "ent of 0-500 mM NaCl to elute PDE isozymes . . . " instead of "ent of 0-500 NaCl to elute PDE isozymes . . .". Please see page 8, lines 23-24 of WO2008/026156 originally submitted with this application on September 5, 2012.

In line 16 of paragraph [0039], "5 in M $MgCl_2$ . . . " appears instead of "5 mM $MgCl_2$ . . . ". Please see page 8, line 27 of WO2008/026156 originally submitted with this application on September 5, 2012.

In line 20 of paragraph [0039], "reacted in the incubator of 30° C. for about 1 hour and the . . . " should read, "reacted in the incubator of 30° C for about 1 hour and the . . . ". Please see page 8, line 30 of WO2008/026156 originally submitted with this application on September 5, 2012.

In line 25 of paragraph [0039], "reacted in an incubator at 37° C. for 10 min and chilled in an . . . " should read, "reacted in an incubator at 37° C for 10 min and chilled in an . . . ". Please see page 9, line 3 of WO2008/026156 originally submitted with this application on September 5, 2012.

In line 31 of paragraph [0039), "tube with vortexing. The mixture is left at 4° C. for 15 min . . . " should read, "tube with vortexing. The mixture is left at 4° C for 15 min . . . ". Please see page 9, line 7 of WO2008/026156 originally submitted with this application on September 5, 2012.

In claim 12, in the line below formula (I), the word "least" is missing at the end of the line. Therefore, claim 12, in the line below formula (I) should read, "in free or pharmaceutically acceptable salt form, and at least one" instead of "in free or pharmaceutically acceptable salt form, and at one". Please see page 4, claim 12 of the Preliminary Amendment originally submitted with this application on September 5, 2012.

In line 7 of claim 13, the word "in" is missing. Therefore, the line that reads "one sildenafil or tadalafil, free or pharmaceutically acceptable" should read, "one sildenafil or tadalafil, in free or pharmaceutically acceptable". Please see page 5, claim 13 of the Preliminary Amendment originally submitted with this application on September 5, 2012.

In line 7 of claim 14, "one sildenafil or tadalafil, is free or pharmaceutically accept-" should read, "one sildenafil or tadalafil, in free or pharmaceutically accept-". Please see page 5, claim 14 of the Preliminary Amendment originally submitted with this application on September 5, 2012.

Please also insert the word "Claims" after "Example 3" and before claim 1 on page 4 of the published application to separate the claims from the examples. Please see page 11 of WO2008/026156 originally submitted with this application on September 5, 2012

The record on public PAIR clearly shows that the specification and claims submitted with the filing of this application on September 5, 2012 did not contain these errors. Applicants hereby request corrected publication of the application with the corrections noted above. As this Request for Corrected Publication is filed within two months of the publication date, it is believed that no fee is due. However, if this is incorrect, the Commissioner is authorized to charge any additional fees to deposit account No. 50-4255.

UNITED THERAPEUTICS CORP., EX1006, page 69
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Respectfully submitted,

Date March 4, 2013 /Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, NJ 07041
973-912-5232 phone
973-912-5236 fax

UNITED THERAPEUTICS CORP., EX1006, page 70
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

US 20130005734A1

(19) United States

(12) Patent Application Publication

CLOZEL

(10) Pub. No.: US 2013/0005734 A1

(43) Pub. Date: Jan. 3, 2013

(54) THERAPEUTIC COMPOSITIONS

(75) Inventor: Martine CLOZEL, Binningen (CH)

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

(21) Appl. No.: 13/604,148

(22) Filed: Sep. 6, 2012

Related U.S. Application Data

(63) Continuation of application No. 12/439,290, filed on Feb. 27, 2009, now Pat. No. 8,268,847, filed as application No. PCT/IB2007/053448 on Aug. 28, 2007.

(30) Foreign Application Priority Data

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

Publication Classification

(51) Int. Cl.

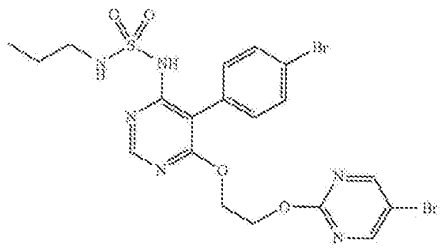
A61K 31/506	(2006.01)
A61P 9/12	(2006.01)
A61K 31/519	(2006.01)

(52) U.S. Cl. 514/250; 514/252.16; 514/274

(57) ABSTRACT

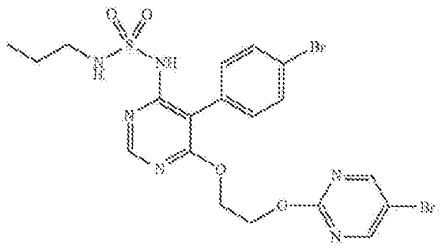
The invention relates to a product containing the compound of formula (I) below (I) or a pharmaceutically acceptable salt of this compound, in combination with at least one compound having PDE5-inhibitory properties, or a pharmaceutically acceptable salt thereof, for therapeutic use, simultaneously, separately or over a period of time, in the treatment of a disease wherein vasoconstriction is involved.

(I)



THERAPEUTIC COMPOSITIONS

[0001] 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.

[0002] 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).

[0003] PDE-5 inhibitors have been notably described in the following patent documents:

- [0004] 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 1 097 711 (describing i.a. sildenafil for pulmonary hypertension);
- [0005] WO 99/24433 (describing i.a. vardenafil as well as the use of the same for i.a. hypertension, angina pectoris and erectile dysfunction);
- [0006] 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);
- [0007] WO 00/27848 (describing i.a. udenafil and the use thereof for impotence).

[0008] 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.

[0009] 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.

[0010] 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.

[0011] "PDE-5" stands in the present application for cyclic guanosine 3',5'-monophosphate (cGMP) phosphodiesterase type 5.

[0012] "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.

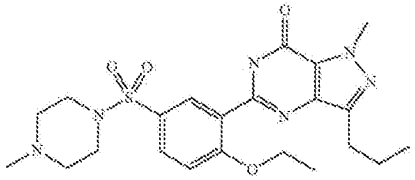
[0013] "Separately" or "separate", when referring to a therapeutic use, means in the present application that the therapeutic use concerned consists in the administration of two or more active ingredients at approximately the same time by at least two different routes.

[0014] 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.

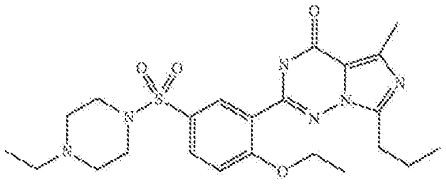
[0015] By "disease wherein vasoconstriction is involved" is meant in particular hypertension, pulmonary hypertension (including pulmonary arterial hypertension), diabetic arteriopathy, heart failure, erectile dysfunction or angina pectoris.

[0016] 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.

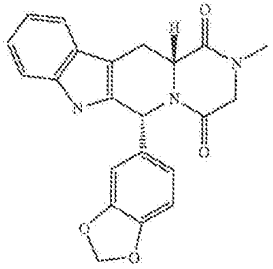
[0017] Specific examples of compounds having PDE5-inhibitory properties include the compounds having the following structures (names):



(sildenafil)



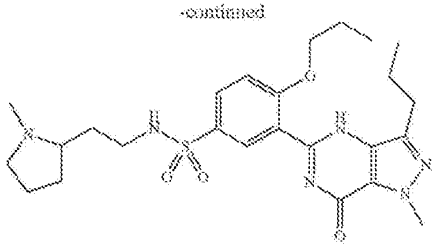
(vardenafil)



(tadalafil)

UNITED THERAPEUTICS CORP., EX1006, page 72
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

-continued



(sildenafil)

[0018] 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.

[0019] 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.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] 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).

[0024] 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.

[0025] According to one particularly preferred variant of the invention the compound having PDE5-inhibitory properties will be sildenafil.

[0026] According to another particularly preferred variant of the invention the compound having PDE5-inhibitory properties will be tadalafil.

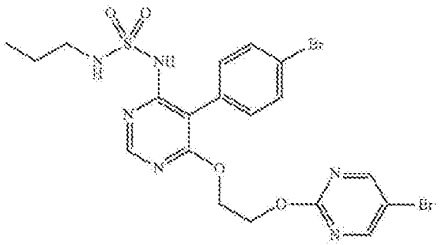
[0027] The administration route of the compound of formula (I) and that of the compound having PDE5-inhibitory properties is preferably the same. In particular, the common administration route for the compound of formula (I) and for the compound having PDE5-inhibitory properties will be the intravenous or oral route (and notably the oral route).

[0028] 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.

[0029] 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).

[0030] The invention also relates to a pharmaceutical composition containing, as active principles, the compound of formula (I) below

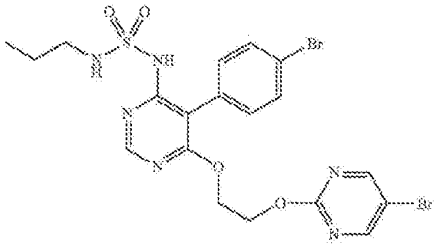
(I)



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.

[0031] 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.

[0032] Besides, preferences indicated for the product according to this invention of course apply mutatis mutandis to the pharmaceutical compositions and uses of this invention.

[0033] 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

[0034] 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

[0035] The experimental methods described hereafter can be used to show the pharmacological properties of the invention compounds.

Dahl Salt-Sensitive Rat Model

[0036] 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).

[0037] 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

[0038] 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}:

[0039] 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 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 in M $MgCl_2$, 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, AG1-X2, 200-400 mesh) which has been already washed with 0.5N HCl, H_2O, 0.5N NaOH, H_2O, 0.5N HCl 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.

[0040] 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

[0041] 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

[0042] Following the test protocol described previously in the part entitled "Spontaneously hypertensive rat model",

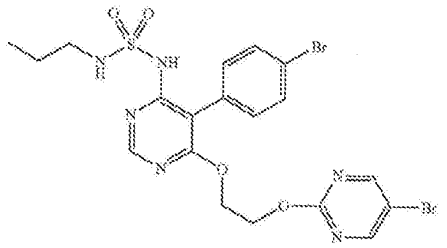
oral administration of the compound of formula (I) and tadalafil decreased blood pressure in SHR rats: the compound of formula (I) (0.3 mg/kg) decreased blood pressure with an ABC of 44 and tadalafil (10 mg/kg) with an ABC of 286. The ABC after oral gavage of the combination (compound of formula (I)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

Example 3

[0043] 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.

1. A method for the treatment of hypertension, pulmonary hypertension or pulmonary arterial by 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 PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously

3. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

6. The method according to claim 5, wherein said administration will not exceed one day.

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

8. The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

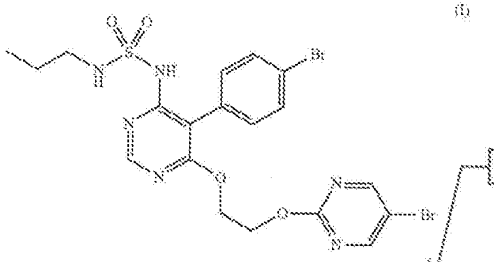
9. The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

(I)

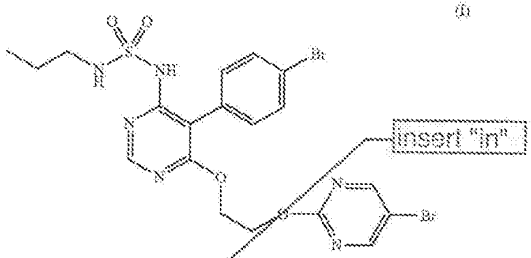


insert "least"

in free or pharmaceutically acceptable salt form, and at one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

13. A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

(I)

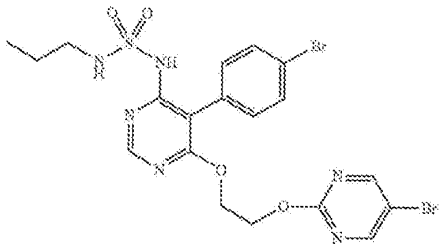


insert "in"

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, free or pharmaceutically acceptable salt form.

14. A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):

(I)



in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, is free or pharmaceutically acceptable salt form.

* * * * *

Electronic Acknowledgement Receipt	
EFS ID:	15111668
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La/Dave O'Brien
Filer Authorized By:	Brittany La
Attorney Docket Number:	AC-66-USC
Receipt Date:	04-MAR-2013
Filing Date:	05-SEP-2012
Time Stamp:	17:37:47
Application Type:	Utility under 35 USC 111(a)

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	Request/Corrected Patent Application Publications	AC-66-USC_Request_for_Republication_Revised.pdf	76322 82e8e34c954b461fdbb81600ce1a2bf3b44dce32	no	3

Warnings:
Information:

2	Request/Corrected Patent Application Publications	AC-66-USC_Marked_up_publication.pdf	2409729 99916fcc5f58e1dc750a21b7ef4946ebc0776024	no	5

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

Total Files Size (in bytes):	2486051

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.

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.

Document Code: IMIS
Document Date: Date IMIS received at FEP

Correction Authorization

Application Number: 13604148

To: Patent Data Capture Contractor

Re: Request for Correction

- ☒ **PGA9 dated** 3-4-13
- ☐ **Other applicant request (attached)**
- ☐ **PTO internal request (attached)**

Please review the document indicated above.

The USPTO authorizes the data capture contractor to make any appropriate changes necessary to correct errors to source only in the specification, claims, abstract and/or drawings. These changes should be incorporated in the patent grant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

RESPONSE UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the non-final Office Action mailed January 9, 2013, the shortened statutory period for response ending April 9, 2013, Applicant provides the following remarks.

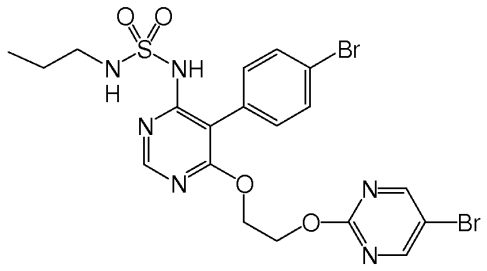
Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Listing of the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Previously Presented) 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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. (Previously Presented) The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound

UNITED THERAPEUTICS CORP., EX1006, page 80
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

6. (Previously Presented) The method according to claim 5, wherein said administration will not exceed one day.

7. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

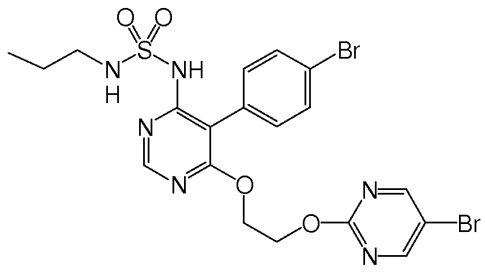
8. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

9. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. (Previously Presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

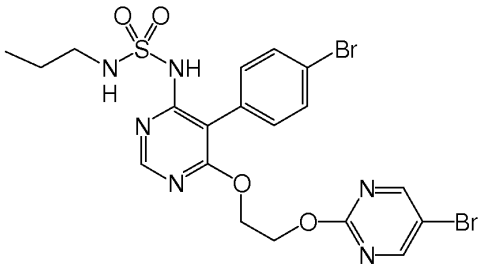


(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 81
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

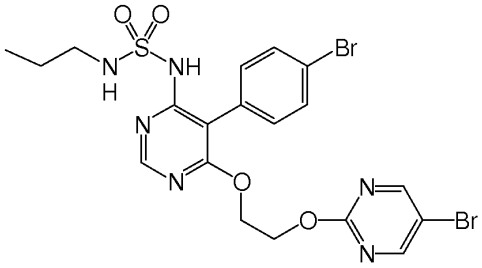
13. (Previously Presented) A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. (Previously Presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 82
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Remarks

Claims 1-14 are pending in this application. Claims 1-14 stand rejected. There are no amendments to the claims.

Applicant thanks the Examiner for the courtesy afforded in the interview conducted on January 9, 2013 with Applicant's undersigned attorney and Sreeni Padmanabhan. In addition to the summary of the interview mailed January 17, 2013, Applicant adds that also discussed during the interview is that the Keyser reference teaches away from the invention because Keyser teaches away from the use of a dual ET_A/ET_B antagonist, particularly compounds with ET_B antagonistic activity. There is no rationale for selecting compound 104 over those disclosed in Table 1 of Bolli et al. which have low IC_{50} for ET_A and very high IC_{50} for ET_B. Several of these issues will be described in further detail below.

Information Disclosure Statement

The Office Action states that Applicant's Information Disclosure Statement filed September 5, 2012 failed to comply with 37 C.F.R. 1.98(a)(2) because certain references were not supplied. Applicant submits herewith a Supplemental Information Disclosure Statement with copies of the references EP 0743307, EP 0658548 and Iglarz et al., and respectfully requests consideration of the same by the Office.

Rejection under 35 U.S.C. § 103(a)

Claims 1-14 are rejected under 35 U.S.C. § 103 for alleged obviousness over International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") in view of International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). Applicant respectfully traverses the rejection.

The Office Action at pages 12-13 asserts that Bolli teaches the instant compound as an ET antagonist 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, portal hypertension, pulmonary hypertension and erectile dysfunction. The Office Action further asserts that Keyser teaches that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension, and that pulmonary hypertension "relates to pulmonary arterial hypertension" (citing Keyser at paragraph 43). The

UNITED THERAPEUTICS CORP., EX1006, page 83
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Office Action then concludes that it would have been "obvious and motivated" to combine the compound of Formula I disclosed in Applicant's claims 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 teaches that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension. Applicant respectfully disagrees that the present invention is obvious over combination of Bolli and Keyser.

The Federal Circuit has specifically held that the framework for analysis as to the obviousness of chemical formulations involves a "lead-modification" analysis similar to that involving novel compounds. *Unigene Laboratories, Inc. et al. v. Apotex, Inc., et al.,* 655 F.3d 1352, 1361-1362 (Fed. Cir. 2011), applying the analytical framework of *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.,* 492 F.3d 1350, 1356 (Fed. Cir. 2007) and its progeny. First, a lead or reference formulation is identified from the art, and then a flexible teaching-suggestion-motivation (TSM) test is applied to determine whether there is reason or motivation to modify the lead formulation to make the claimed invention with a reasonable expectation of success. *Id. See also, Ex parte Subramanyam, et al.,* B.P.A.I. Decision January 15, 2010, Appeal No. 2009-012300 pp. 7-8; *Ex parte Subramanyam*, B.P.A.I. Decision March 29, 2010, Appeal No. 2010-002463. *Unigene* elaborates on the well-established principle that neither general disclosures nor mere identification in the prior art of each component of a composition can establish that the combination as a whole would have been obvious. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (emphasis added). As the Supreme Court held in *KSR*, "it will be necessary . . . to determine whether there was an apparent reason to combine [or modify] the known elements [in the prior art] in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR Int'l., Co. v. Teleflex, Inc*., 127 S. Ct. 1727, 1740 – 1741 (2007).

The Keyser Reference

As discussed in the interview, Keyser is directed to combination therapy comprising an endothelin A receptor (ET_A) antagonist and a phosphodiesterase 5 (PDE5) inhibitor for treatment and/or prevention of pulmonary arterial hypertension (PAH). Keyser discusses the two types of mammalian ET receptors (ET_A and ET_B) and the importance of ET_A selectivity for its combination

UNITED THERAPEUTICS CORP., EX1006, page 84
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

therapy at, for example, paragraphs [0029], [053]-[059], and [068]-[069]. For example, at paragraph [029] Keyser states that for each of its recited embodiments:

> ". . . the ETA antagonist may be selected from any one of the compounds described herein **selective for the endothelin A receptor** . . ." (emphasis added)

Keyser further states at paragraph [059] that:

> 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**. (emphasis added)

Keyser further states at paragraph [069] that:

> 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. (emphasis added).

Thus, the use of an ET_A-selective antagonist (with little or no antagonistic activity on ET_B) is a fundamental aspect of the Keyser teaching.

The Bolli Reference

Bolli discloses over 200 examples of novel sulfamide compounds having ET_A receptor and ET_B receptor antagonistic activities useful for, e.g., vasoconstriction, proliferation or inflammation due to endothelin. Table 1, on pages 4-8 discloses competitive inhibition (IC_{50}) data for ET_A and ET_B receptor inhibition for more than 130 of its disclosed compounds. Although Bolli shows the compound of Formula I described in the present claims on page 28, Bolli does not provide data for that compound.

The present invention is not obvious over the disclosures of Bolli and Keyser

a) There is no legally sufficient motivation to select the compound of Applicant's claims from Bolli

UNITED THERAPEUTICS CORP., EX1006, page 85
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Contrary to the assertion of the Office Action, those of skill in the art would not have been led to use the compound described in Applicant's claims into the Keyser formulation. As demonstrated above, Keyser ***explicitly*** teaches the use of ***ET_A-selective antagonists*** in its combination therapy. The art-skilled, presented with Bolli, would have no motivation whatsoever to choose the compound of Formula I for use in Keyser, for at least the reasons that Bolli does not provide data regarding either 1) the ET_A-binding activity of the compound; or 2) the ET_A-ET_B selectivity of the compound. Thus, selecting the compound of Applicant's claims from Bolli would require choosing it from among the over 200 Bolli examples, without the benefit of any ET_A and ET_B inhibition data, despite the presence in Bolli of 134 compounds that did have ET_A-ET_B binding data. Clearly, such a selection could only be made using impermissible hindsight, with Applicant's disclosure as a guide.

In the interview, it was suggested by the Examiner that Bolli compound 104, which is the N-ethyl analog of the compound of Formula I, is the closest art and that it would be obvious to go from the ethyl to the n-propyl thereby arriving at the compound of Formula (I) claimed the current invention. However, Applicant respectfully points out that there are a number of compounds disclosed in Bolli that would be superior candidates in accordance with the Keyser teachings. See for example, the compounds of Bolli Examples 12, 26, 34, 109, 110, 115, 117, 118, 193 and 214. Given the numerous compounds in Bolli suitable for use in Keyser, there is no motivation to select compound 104 of Bolli. as the lead compound.

Moreover, even if compound 104 was a proper lead compound under the *Unigene* analysis (and it is most emphatically not), there is no motivation whatsoever to modify it to achieve the compound of Applicant's claims, and, even if one were to do so, there would be no reasonable expectation of success.

Thus, as discussed above and in the interview, it cannot be fairly said that there would have been any legally sufficient motivation to select the compound of Formula I from the Bolli reference for use in the Keyser combination therapy. In the absence of such legally sufficient motivation, the present rejection cannot be maintained, and should be withdrawn for this reason alone.

b) Keyser teaches away from using a dual ET_A-ET_B receptor antagonist, such as the compound of Formula I

UNITED THERAPEUTICS CORP., EX1006, page 86
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Moreover, Keyser teaches away from the present invention. Keyser discusses combination therapy, particularly with PDE5 inhibitors, at pages 19-20, paragraphs [067]-[068]. Keyser states that the use of a non-selective ET receptor antagonist (such as bosentan) "interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complimentary fashion for the multiple pathways . . . to provide superior efficacy and/or dosage regimes and/or reduction in side effects". Keyser, paragraph [067]. Specifically, Keyser explains that:

> . . . 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 tum activates the guanyl cyclase which increases 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. (emphasis added)

Thus, Keyser teaches away from the use of non-selective antagonists, particularly compound that also antagonizes ET_B, such as bosentan, and, as discussed below, the compound of Formula I described in Applicant's claims.

In this regard, Applicant respectfully directs the Examiner's attention to Iglarz et al., Journal of Pharmacology and Experimental Therapeutics, Vol. 329, No. 3 (2008) ("Iglarz"), a copy of which is provided herewith, and listed in Applicants Information Disclosure Statement, also filed herewith. Iglarz describes a study of the pharmacology of macitentan, which is the compound of Formula I listed in Applicant's present claims. Iglarz discusses on page 740 an *in vivo* pharmacology study comparing the ET_A-ET_B receptor blocking properties of the two compounds. Iglarz states:

UNITED THERAPEUTICS CORP., EX1006, page 87
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

> In Vivo Pharmacology Studies. Macitentan is best studied in vivo because this allows the study of the overall pharmacological effects of macitentan together with its metabolite. When administered to normotensive rats, **macitentan, like bosentan, increased plasma ET-1 concentration, confirming its dual blockade on both ET_A and ET_B receptors**. This increase occurred at a 10-fold lower dose than with bosentan, indicating a more portent pharmacological activity in vivo (Fig. 2). (emphasis added)

Thus, macitentan (or the compound of formula (I) of the current invention), like bosentan, is a dual ET_A-ET_B receptor antagonist. Given the explicit disclosure in Keyser of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A-ET_B receptor antagonists such as bosentan, it can be seen that Keyser teaches away from the use of macitentan in its combination therapy. Accordingly, Applicant respectfully asserts that the rejection should be withdrawn for this additional reason.

c) The present invention produces an unexpected and synergistic effect

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

The present specification provides at pages 7-10 Examples wherein the association of macitentan, administered orally at a dose of 0.3 mg/kg, with tadalafil, administered orally at a dose of 10 mg/kg, was studied in two different hypertension models: the Dahl salt-sensitive rat model (Example 1) and the spontaneously hypertensive rat model (Example 2). In addition, the association of macitentan, administered orally at a dose of 0.3 mg/kg, with sildenafil, administered orally at a dose of 30 mg/kg, was studied in the spontaneously hypertensive rat model (Example 3). Arterial blood pressure curves were obtained for administration of macitentan alone, the PDE5 inhibitor (tadalafil or sildenafil) alone, and the combination of macitentan and the PDE5 inhibitor. 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. As the specification explains, the higher the ABC, the stronger the effect of the item tested for lowering blood pressure. See the specification at page 7,

UNITED THERAPEUTICS CORP., EX1006, page 88
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

line 10 to page 8, line 11. The results, shown in the specification, are summarized in the Table below:

Example	Model	PDE5 Inhibitor	ABC for PDE5 Inhibitor	ABC for Macitentan	ABC for PDE5 Inhibitor + Macitentan
1	Dahl salt-sensitive rat Model	Tadalafil	310	256	923
2	Spontaneously 25 hypertensive rat model	Tadalafil	286	44	444
3	Spontaneously 25 hypertensive rat model	Sildenafil	229	38	317

It can be seen that in all three Examples, the combination of the PDE5 inhibitor and the compound of Formula I (macitentan) provided ABC values that were unexpected; i.e., greater than the sum of the ABC values for administration of either component alone. There is no suggestion of any such synergy in the prior art, and especially in the Keyser (and/or Bolli) reference, which, as discussed above, teaches away from the present invention. Accordingly, the invention of the present claims provides synergistic and unexpected results, and is not obvious over the Bolli and Keyser references for this additional reason.

In view of the preceding remarks, Applicant respectfully asserts that the present invention is not obvious in view of the combination of Bolli and Keyser, and respectfully requests withdrawal of this rejection.

Double Patenting Rejections

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser").

As best understood, the Office Action appears to base its rejection on the same rationale as the instant rejection under U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser.

UNITED THERAPEUTICS CORP., EX1006, page 89
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

However, as discussed in detail above, Applicant asserts that the present invention is not obvious in view of the Bolli and Keyser references. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection for precisely the same reasons as set forth above in Applicant's response to the present rejection under U.S.C. § 103.

Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142 ("the '142 application") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). Applicant notes that the '142 application has now issued as U.S. Patent No. 8,367,685.

The Office Action states that the '142 application (now the '685 patent) teaches the compound of Formula I to treat pulmonary arterial hypertension, and admits that the '685 patent does not teach "the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary hypertension, nor the administration schedule of claims 2-6 and 12-14." Office Action at page 6. The Office Action then asserts that it would be obvious to combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary 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 combined to treat pulmonary hypertension." Office Action at page 7.

Thus, the Office Action again appears to base its rejection on the same rationale as the instant rejection under U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser. However, as discussed in detail above, Applicant asserts that the present invention is not obvious in view of the Bolli and Keyser references. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection for precisely the same reasons as set forth above in Applicant's response to the present rejection under U.S.C. § 103.

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of U.S. Patent No. 8,268,847 ("the '847 patent") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). The present application is a continuation of the application leading to the '847 patent. Applicant will consider providing further argument or filing a terminal disclaimer over the '847 patent upon an indication of otherwise allowable subject matter in the present application.

UNITED THERAPEUTICS CORP., EX1006, page 90
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional fees, or credit any overpayment, to Deposit Account No. 50-4255.

Respectfully submitted,

Date April 9, 2013

/Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, NJ 07041
973-912-5232 phone
973-912-5236 fax

UNITED THERAPEUTICS CORP., EX1006, page 91
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Brittany La
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	15474606
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La
Filer Authorized By:	
Attorney Docket Number:	AC-66-USC
Receipt Date:	09-APR-2013
Filing Date:	05-SEP-2012
Time Stamp:	21:19:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	6330
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		AC-66-USC_SIDS_04092013.pdf	144553 bbc9e1e726a28d02e8109f9eb5ab01035283d8ad	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
2	Foreign Reference	EP_0743307.pdf	2402447 5f7f0e48a6c4c2c992e675e52dbc6915909f9823	no	63
Warnings:					
Information:					
3	Foreign Reference	EP_0658548.pdf	702198 e81129565c5543c840738789 07a3f8534321fae0	no	74
Warnings:					
Information:					
4	Non Patent Literature	Iglarz_et_al_Pharmacology_Macitentan_Endothelin_Receptor_Antagonist.pdf	1014662 8d3988482dced682227b3580ffef83beaaf29d1d	no	10
Warnings:					
Information:					
5	Amendment/Req. Reconsideration-After Non-Final Reject	AC-66-USC_response_to_OA_mailed_jan_9_2013.pdf	86233 adac3bdcf9a87424be8cb9db3eb48875bbd241c2	no	13
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	30124 1ef745a1dd76aa1741653ac5c56fadbd9fb24017	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4380217	

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.

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.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicant respectfully requests that this Information Disclosure Statement be entered and the documents listed on the attached form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

The filing of this Information Disclosure Statement is not be be construed as a representation that a search has been made, nor construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability or prior art.

Pursuant to 37 C.F.R. §1.98(a), copies of references which are non US patents and patent applications are enclosed herein.

Attached is the required fee in the amount of $180.00 in order to have this Information Disclosure Statement considered.

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §1.97(b), it is believed that no other fee or statement is required with the Information Disclosure Statement. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), please charge the same to Deposit Account 50-4255. If there are any questions relating to fee payments associated with this application, please contact the undersigned attorney at the contact information listed below.

Respectfully submitted,

Date: April 9, 2013

By: S:/Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, New Jersey 07041
973-912-5232
973-912-5236 (fax)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 1 of 1	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		EP 0743307	11/20/1996	Tanabe Seiyaku Co., Ltd.	
		EP 0658548	12/15/1994	Tanabe Seiyaku Co., Ltd.	

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
		IGLARZ, M., et al., "Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 327, No. 3, pp. 736-745, (2008).	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/604,148	Filing Date 09/05/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/09/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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.

LIE
/RUTH LLOYD/

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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC

CONFIRMATION NO. 5499

50446
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

PUB REQUEST ACCEPTANCE LETTER

OC000000061118531

Date Mailed: 05/10/2013

NOTICE OF ACCEPTANCE OF PUBLICATION REQUEST

The request for voluntary publication, amended publication, early publication, redacted publication, republication, corrected publication or revised publication has been received for this application. The request, including payment of any necessary fee(s), is in compliance with 37 CFR 1.215, 1.217, 1.219 or 1.221.

The projected publication date is 08/15/2013.

/dterry/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED THERAPEUTICS CORP., EX1006, page 101
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

MAILED

MAY 16 2013

OFFICE OF PETITIONS

Applicant: Martine Clozel
Appl. No.: 13/604,148
Filing Date: September 5, 2012
Title: THERAPEUTIC COMPOSITIONS
Attorney Docket: AC-66-USC
Pub. No.: US 2013/0005734 A1
Pub. Date: January 3, 2013

This is a decision on the request for a corrected patent application publication under 37 CFR 1.221(b), received on March 4, 2013, for the above-identified application.

The request is GRANTED.

The corrected patent application publication will be published in due course, unless the patent issues before the application is republished.

Inquiries relating to this matter may be directed to Sherry D. Brinkley at (571) 272-3204.

/Christopher Bottorff/

Christopher Bottorff
Petitions Examiner
Office of Petitions

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 06/20/2013

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 301
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/20/2013	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com
Hoxie@blackhillsip.com

Office Action Summary	Application No. 13/604,148	Applicant(s) CLOZEL, MARTINE	
	Examiner KENDRA D. CARTER	Art Unit 1627	AIA (First Inventor to File) Status No

-- 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 *9 April 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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) *1-14* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-14* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

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).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/13*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the applicant's remarks and arguments of April 9, 2013 made to the office action filed January 9, 2013. Claims 1-14 are pending. No claim amendments have been made.

For the reasons in the previous office action and below, the Applicant's arguments of all previous rejections were found not persuasive, thus the rejections are upheld.

The Applicant's arguments are addressed below.

Information Disclosure Statement

The information disclosure statement filed April 9, 2013 has been considered.

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 1-14 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 or sildenafil to treat pulmonary hypertension or pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not

exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be 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 combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

2) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 10 and 18 of copending Application No. 12/388,142 ('142) (recently allowed) 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 to treat pulmonary arterial hypertension.

The Application '142 does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary 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 combined to treat pulmonary hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or

three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

3) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent 8,268,847 ('847) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

The Patent '847 teaches a composition of formula I with a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary hypertension.

The Patent '847 does not teach the treatment of pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to treat pulmonary arterial hypertension with the combination because Keyser et al. teach that an ET antagonist

and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

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 1-14 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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Bolli et al. does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious and motivated 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 combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

To one skilled in the art it would be obvious and motivated to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

> The Applicant argues that the Federal Circuit has specifically held that the framework for analysis as to the obviousness of chemical formulations involves a "lead-modification" analysis similar to that involving novel compounds. First, a lead or reference formulation is identified from the art, and then a flexible teaching-suggestion-motivation test is applied to determine whether there is a reason or motivation to modify the lead formulation to make the claimed invention with a reasonable expectation of success. Unigene elaborates on the well-established principle that neither general disclosures nor mere identification in the prior art of each component of a composition can establish that the combination as a whole would have been obvious.

The Examiner has shown that first the claimed compound is taught to be a ET antagonist that can be combined with other active agents to treat conditions such as hypertension and pulmonary hypertension (see Bolli et al.). Second, Keyser et al. teaches the specific combination of a ETA antagonist and PDE5-inhibitor for the treatment of conditions such as hypertension and pulmonary hypertension. Thus, it is known that the combination of a ET antagonist and PDE5-inhibitor can be used to treat hypertension and pulmonary hypertension. Therefore, one skilled in the art would expect with high levels of success that the ET antagonists of Bolli et al., specifically those compounds that fall within the definition of ET antagonists of Keyser et al., can be used in the combination with PDE5-inhibitors to treat the same disorder. Selection of a known material based on its suitability for its intended use is obvious absent a clear

showing of unexpected results attributable to the Applicant's specific selection. See e.g., *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960).

> The Applicant argues that Keyser teaching is for the use of an ET_A-selective antagonist with little or no antagonistic activity on ET_B as a fundamental aspect. Particularly, Keyser teaches away from the use of non-selective antagonists such as bosentan. Iglarz et al. teaches that macitentan, like bosentan, increased plasma ET1 concentration, confirming its dual blockade on both ET_A and ET_B receptors. The Bolli reference discloses over 200 examples having ET_A receptor and ET_B receptor antagonistic activities. Although Bolli shows the compound of Formula I described in the present claims on page 28, Bolli does not provide data for that compound. There is no legally sufficient motivation to select the compound of Applicant's claims from Bolli without impermissible hindsight. In the interview, it was suggested by the Examiner that Bolli compound 104 is the closest compound (because it has a N-ethyl versus a N-propyl) that is provided that gives its ET_A and ET_B receptor antagonistic activities and that it would be obvious to make the homolog of compound 104 because of it would be expected to have similar properties. Given the numerous compounds of Bolli suitable for use in Keyser, there is no motivation to select compound 104 of Bolli or its homologs as the lead compound. Further, the present invention produces an unexpected and synergistic effect. Lastly, the Applicants respectfully requests reconsideration and withdrawal of the rejections including the double patenting rejections for the reasons above.

The Examiner disagrees because Keyser et al. defines selective compounds for ET_A antagonist should display a relative receptor binding ratio of at least 100 (see paragraph 59). Keyser et al. also teaches that bosentan is considered nonselective because it has an ET_A:ET_B selectivity ratio of 20 (see paragraph 60). According to Bolli et al. the ethyl analog of the Applicants claimed compound has a ET_A:ET_B selectivity ratio of 682.95 (see page 93, compound 104; and page 6). Thus, the compound is much more selective for ET_A than ET_B, far from being considered as nonselective

compared to bosentan, and fits the definition of an ET_A antagonist by Keyser et al. Further, one skilled in the art would be motivated to choose all the compounds of Bolli et al. that have greater selectivity for ET_A over ET_B with reasonable expectation of success and motivation that the combination with a PDE5 inhibitor would provide treatment for conditions such as hypertension and pulmonary hypertension. Selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the Applicant's specific selection. See e.g., *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960). Although the specific claimed compound is taught by Bolli et al. but not tested for its ET_A:ET_B selectivity ratio one would expect it to be similar to the N-ethyl analog compound 104. Compounds with are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by –CH2- groups are generally of sufficiently close structural similarity that there is presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457,195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d1082,197USPQ 601 (CCPA 1978). With regard to the unexpected and synergistic results, one 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 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.

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 9:30 am - 6:00 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

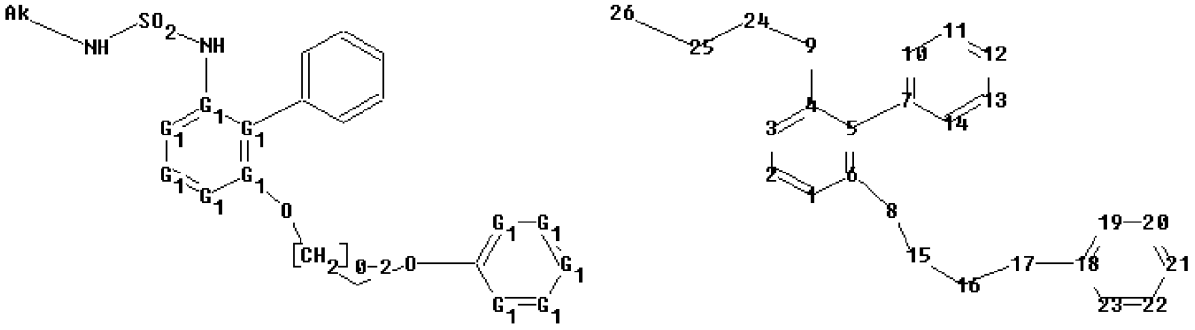
number for the organization where this application or proceeding is assigned is 571-273-8300.

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

Uploading C:\Users\kcarter\Documents\STN Express 8.4\Queries\13604148A.str



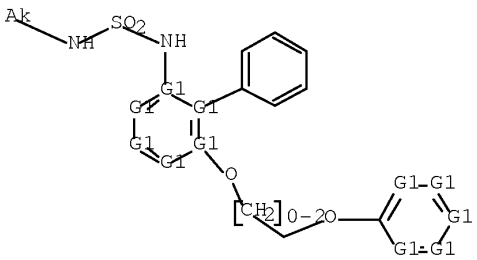
chain nodes :
8 9 15 16 17 24 25 26
ring nodes :
1 2 3 4 5 6 7 10 11 12 13 14 18 19 20 21 22 23
chain bonds :
4-9 5-7 6-8 8-15 9-24 15-16 16-17 17-18 24-25 25-26
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-10 7-14 10-11 11-12 12-13 13-14 18-19 18-23
19-20 20-21 21-22 22-23
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 4-9 5-6 5-7 6-8 8-15 9-24 15-16 16-17 17-18 18-19
18-23 19-20 20-21 21-22 22-23 24-25 25-26
normalized bonds :
7-10 7-14 10-11 11-12 12-13 13-14

G1:C,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:CLASS 9:CLASS 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:CLASS 25:CLASS 26:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1:C,N

Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 12:34:23 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 8999 TO ITERATE

100.0% PROCESSED 8999 ITERATIONS 199 ANSWERS
SEARCH TIME: 00.00.01

L2 199 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 204.29 204.53

FILE 'HCAPLUS' ENTERED AT 12:34:50 ON 12 DEC 2012
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2012 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 12 Dec 2012 VOL 157 ISS 25
FILE LAST UPDATED: 11 Dec 2012 (20121211/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: November 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: November 2012

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the fourth quarter of 2012.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

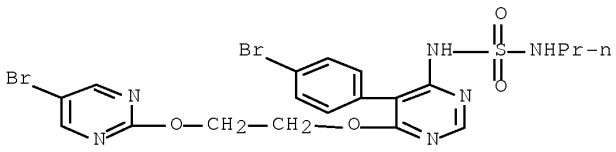
This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 29 L2

=> d ibib hitstr 1-
YOU HAVE REQUESTED DATA FROM 29 ANSWERS - CONTINUE? Y/(N):y

L3 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1480458 HCAPLUS Full-text
DOCUMENT NUMBER: 157:594267
TITLE: New development in endothelin receptor antagonists for pulmonary arterial hypertension

AUTHOR(S): Emoto, Noriaki
CORPORATE SOURCE: Dep. Clin. Pharmacy, Kobe Pharmaceutical University, Japan
SOURCE: Ensho to Men'eki (2012), 20(5), 487-491
CODEN: ENMEFA; ISSN: 0918-8371
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new development of endothelin receptor antagonists for pulmonary arterial hypertension)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



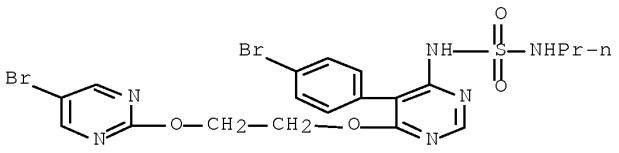
L3 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1477457 HCAPLUS Full-text
DOCUMENT NUMBER: 157:586789
TITLE: Lisuride, terguride and derivatives thereof for use in the prophylaxis and/or treatment of fibrotic changes
INVENTOR(S): Horowski, Reinhard; Palla, Heinz; Tack, Johannes
PATENT ASSIGNEE(S): Sinoxa Pharma UG, Germany
SOURCE: Ger. Offen., 28pp.; Chemical Indexing Equivalent to 156:647621 (WO)
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102010051391	A1	20121011	DE 2010-102010051391	20101111
WO 2012062676	A1	20120518	WO 2011-EP69480	20111104

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD,

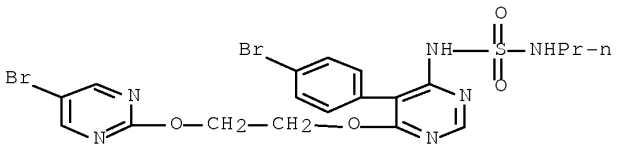
SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: DE 2010-102010051391A 20101111
EP 2011-75179 A 20110727

IT 441798-33-0, Macitentan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lisuride, terguride and derivs. thereof for use in prophylaxis and/or treatment of fibrotic changes)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



L3 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1161225 HCAPLUS Full-text
TITLE: Absorption, distribution, metabolism, and excretion of macitentan, a dual endothelin receptor antagonist, in humans
AUTHOR(S): Bruderer, Shirin; Hopfgartner, Gerard; Seiberling, Michael; Wank, Janine; Sidharta, Patricia N.; Treiber, Alexander; Dingemanse, Jasper
CORPORATE SOURCE: Clinical Pharmacology, Allschwil, Switz.
SOURCE: Xenobiotica (2012), 42(9), 901-910
CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

IT INDEXING IN PROGRESS
IT 441798-33-0, Macitentan
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(absorption, distribution, metabolism, and excretion of macitentan)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN

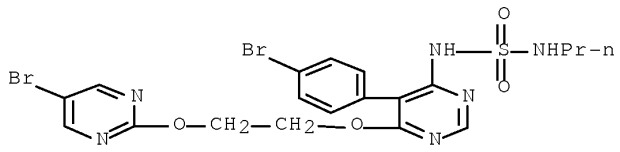
ACCESSION NUMBER: 2012:1156103 HCAPLUS Full-text
DOCUMENT NUMBER: 157:283434
TITLE: Combinations comprising macitentan for the treatment of glioblastoma multiforme
INVENTOR(S): Regenass, Urs
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd., Switz.
SOURCE: PCT Int. Appl., 22pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012104822	A1	20120809	WO 2012-IB50513	20120203

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

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: WO 2011-IB50494 A 20110204
IT 441798-33-0, Macitentan
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations comprising macitentan for treatment of glioblastoma multiforme)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1146863 HCAPLUS Full-text
DOCUMENT NUMBER: 157:372322
TITLE: The Discovery of N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide (Macitentan), an Orally Active, Potent

Dual Endothelin Receptor Antagonist

AUTHOR(S): Bolli, Martin H.; Boss, Christoph; Binkert, Christoph; Buchmann, Stephan; Bur, Daniel; Hess, Patrick; Iglarz, Marc; Meyer, Solange; Rein, Josiane; Rey, Markus; Treiber, Alexander; Clozel, Martine; Fischli, Walter; Weller, Thomas

CORPORATE SOURCE: Drug Discovery Chemistry, Actelion Pharmaceuticals Ltd., Allschwil, CH-4123, Switz.

SOURCE: Journal of Medicinal Chemistry (2012), 55(17), 7849-7861
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

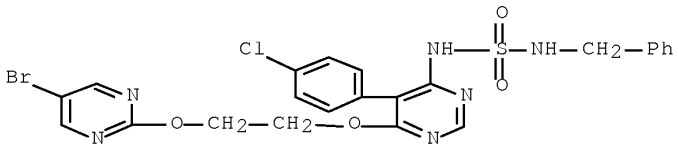
DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

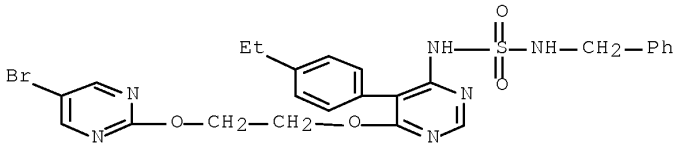
OTHER SOURCE(S): CASREACT 157:372322

IT 441795-23-9P 441795-38-6P 441796-09-4P
441796-13-0P 441798-25-0P 441798-36-3P
441798-39-6P 1393813-57-4P 1393813-58-5P
1393813-59-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(alkyl sulfamide pyrimidines preparation as oral endothelin receptor antagonists and antihypertensives)

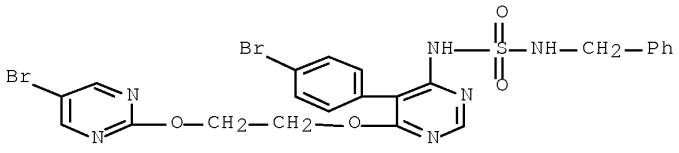
RN 441795-23-9 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



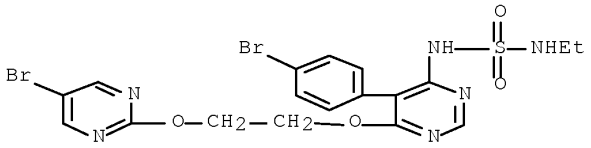
RN 441795-38-6 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-ethylphenyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



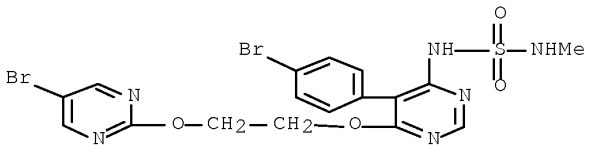
RN 441796-09-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



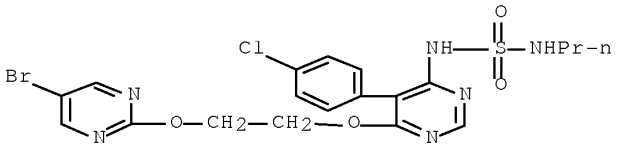
RN 441796-13-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



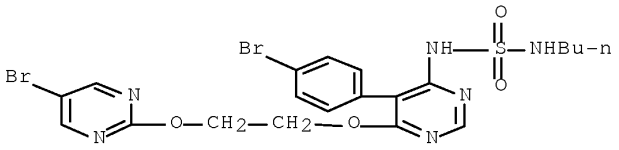
RN 441798-25-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



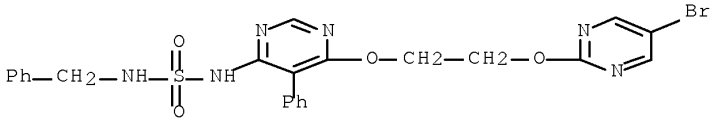
RN 441798-36-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



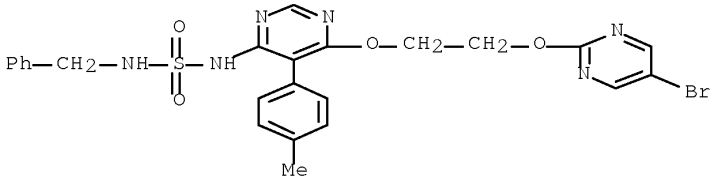
RN 441798-39-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-butyl- (CA INDEX NAME)



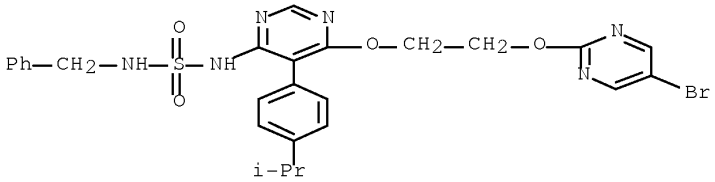
RN 1393813-57-4 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-phenyl-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



RN 1393813-58-5 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)

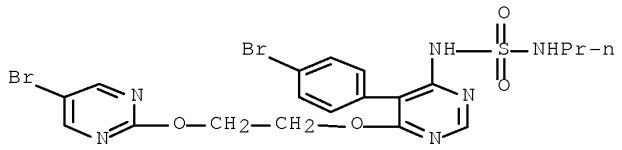


RN 1393813-59-6 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-[4-(1-methylethyl)phenyl]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



IT 441798-33-0P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(alkyl sulfamide pyrimidines preparation as oral endothelin receptor antagonists and antihypertensives)
RN 441798-33-0 HCAPLUS

CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

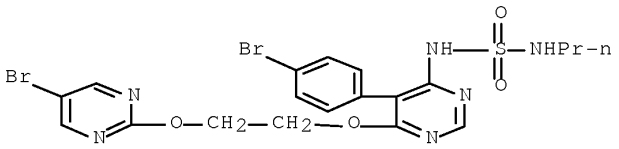


REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:706330 HCAPLUS Full-text
DOCUMENT NUMBER: 156:647621
TITLE: Lisuride, terguride and derivatives thereof for use in the prophylaxis and/or treatment of fibrotic changes
INVENTOR(S): Horowski, Reinhard; Palla, Heinz; Tack, Johannes
PATENT ASSIGNEE(S): Sinoxa Pharma UG, Germany
SOURCE: PCT Int. Appl., 59 pp., Chemical Indexing Equivalent to 157:586789 (DE)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012062676	A1	20120518	WO 2011-EP69480	20111104
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
DE 102010051391	A1	20121011	DE 2010-102010051391	20101111
PRIORITY APPLN. INFO.:			DE 2010-102010051391A	20101111
			EP 2011-75179 A	20110727

OTHER SOURCE(S): MARPAT 156:647621
IT 441798-33-0, Macitentan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lisuride, terguride and derivs. thereof for use in prophylaxis and/or treatment of fibrotic changes)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

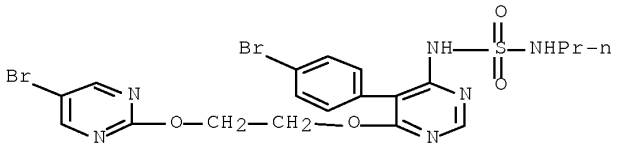


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

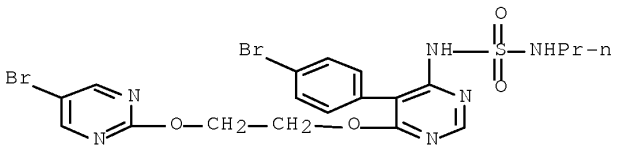
L3 ANSWER 7 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:573697 HCAPLUS Full-text
DOCUMENT NUMBER: 156:552151
TITLE: Combination therapy comprising endothelin A receptor (ERA) antagonists and phosphodiesterase-5 (PDE5) inhibitors for treatment of pulmonary hypertension
INVENTOR(S): Belardinelli, Luiz; Gillies, Hunter Campbell; Liang, Faquan; Shryock, John; Yang, Suya
PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA
SOURCE: PCT Int. Appl., 61pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012051559	A2	20120419	WO 2011-US56404	20111014
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20120269898	A1	20121025	US 2011-274013	20111014
PRIORITY APPLN. INFO.:			US 2010-393529P	P 20101015
			US 2011-490454P	P 20110526
			US 2011-497475P	P 20110615

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy comprising endothelin A receptor (ERA) antagonists and phosphodiesterase-5 (PDE5) inhibitors for treatment of pulmonary hypertension)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



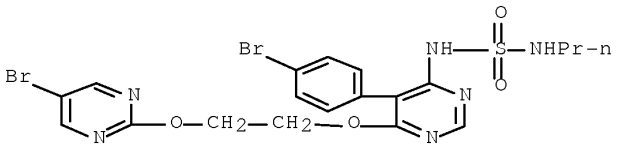
L3 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:305286 HCAPLUS Full-text
DOCUMENT NUMBER: 157:372352
TITLE: Effect of Cyclosporine and Rifampin on the Pharmacokinetics of Macitentan, a Tissue-Targeting Dual Endothelin Receptor Antagonist
AUTHOR(S): Bruderer, Shirin; Aanismaa, Paivi; Homery, Marie-Claude; Hausler, Stephanie; Landskroner, Kyle; Sidharta, Patricia N.; Treiber, Alexander; Dingemanse, Jasper
CORPORATE SOURCE: Clinical Pharmacology, Actelion Pharmaceuticals Ltd, Allschwil, 4123, Switz.
SOURCE: AAPS Journal (2012), 14(1), 68-78
CODEN: AJAOB6; ISSN: 1550-7416
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(effect of cyclosporine and rifampin on the pharmacokinetics of macitentan, a tissue-targeting dual endothelin receptor antagonist)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

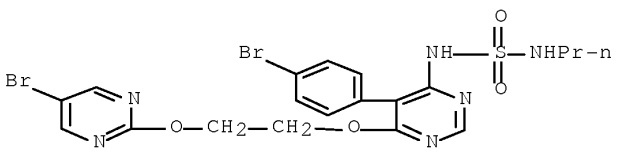
L3 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:248334 HCAPLUS Full-text
DOCUMENT NUMBER: 157:153453
TITLE: Ambrisentan and Tadalafil Synergistically Relax Endothelin-Induced Contraction of Rat Pulmonary Arteries
AUTHOR(S): Liang, Faquan; Yang, Suya; Yao, Lina; Belardinelli, Luiz; Shryock, John
CORPORATE SOURCE: Department of Biology, Gilead Sciences, Inc, Palo

Alto, CA, USA
SOURCE: Hypertension (2012), 59(3), 705-711
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations of tadalafil with bosentan or macitentan relaxed human endothelin-1-induced contraction of rat intrapulmonary artery)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:36836 HCAPLUS Full-text
DOCUMENT NUMBER: 157:184254
TITLE: Therapeutic targets for pulmonary hypertension
AUTHOR(S): Sorbera, L. A.; Rajendran, S.; Dulsat, C.; Forns, N.; Rosa, E.
CORPORATE SOURCE: Thomson Reuters, Barcelona, Spain
SOURCE: Drugs of the Future (2010), 35(11), 947-954
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identifying novel target may be effective in treatment of patient with pulmonary hypertension)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

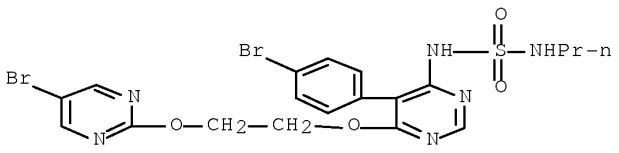


REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1412820 HCAPLUS Full-text
DOCUMENT NUMBER: 155:649078
TITLE: Grape seed proanthocyanidin extracts for treating and preventing pulmonary fibrosis
INVENTOR(S): Na, Seung Won; Cho, Yu Suk; Kwon, Byeong Seok; Jegal, Yang Jin; Ahn, Jong Jun; Seo, Gwang Won
PATENT ASSIGNEE(S): University of Ulsan, Foundation for Industry Cooperation, S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, 8pp.
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

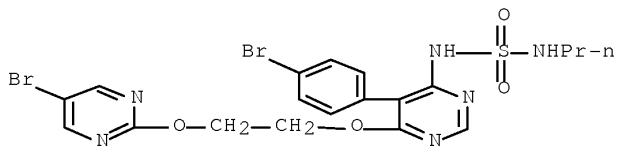
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2011119108	A	20111102	KR 2010-38616	20100426

PRIORITY APPLN. INFO.: KR 2010-38616 20100426
IT 441798-33-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(addnl. drug; grape seed proanthocyanidin exts. for treating and preventing pulmonary fibrosis)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



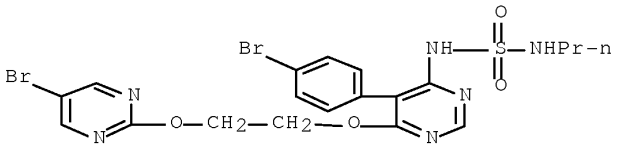
L3 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1381774 HCAPLUS Full-text
DOCUMENT NUMBER: 156:524497
TITLE: Sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression
AUTHOR(S): Kappers, Mariette H. W.; van Esch, Joep H. M.; Smedts, Frank M. M.; de Krijger, Ronald R.; Eechoute, Karel; Mathijssen, Ron H. J.; Sleijfer, Stefan; Leijten, Frank; Danser, A. H. Jan; van den Meiracker, Anton H.; Visser, Theo J.
CORPORATE SOURCE: Divisions of Pharmacology and Vascular Medicine, Erasmus Medical Center, Rotterdam, 8000 CA, Neth.
SOURCE: Journal of Clinical Endocrinology and Metabolism

(2011), 96(10), 3087-3094
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sunitinib-induced hypothyroidism is due to induction of type 3 deiodinase activity and thyroidal capillary regression)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



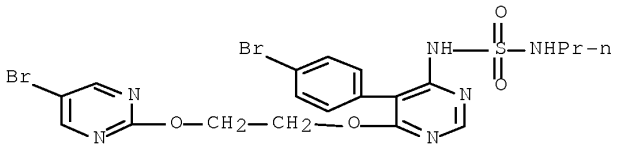
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1161927 HCAPLUS Full-text
DOCUMENT NUMBER: 156:495248
TITLE: Macitentan: entry-into-humans study with a new endothelin receptor antagonist
AUTHOR(S): Sidharta, Patricia N.; Giersbergen, Paul L. M.; Halabi, Atef; Dingemanse, Jasper
CORPORATE SOURCE: Department of Clinical Pharmacology, Actelion Pharmaceuticals Ltd, Allschwil, 4123, Switz.
SOURCE: European Journal of Clinical Pharmacology (2011), 67(10), 977-984
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics, pharmacodynamics, and tolerability of rising single doses of macitentan, endothelin receptor antagonist, in healthy male subjects)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:914748 HCAPLUS Full-text
DOCUMENT NUMBER: 156:328454
TITLE: The Vascular Endothelial Growth Factor Receptor Inhibitor Sunitinib Causes a Preeclampsia-Like Syndrome With Activation of the Endothelin System
AUTHOR(S): Kappers, Mariette H. W.; Smedts, Frank M. M.; Horn, Thomas; van Esch, Joep H. M.; Sleijfer, Stefan; Leijten, Frank; Wesseling, Sebastiaan; Strevens, Helena; Danser, A. H. Jan; van den Meiracker, Anton H.
CORPORATE SOURCE: Division of Pharmacology and Vascular Medicine, Erasmus Medical Center, Rotterdam, 3015 CE, Neth.
SOURCE: Hypertension (2011), 58(2), 295-302
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sunitinib-induced loss of circadian blood pressure rhythm was not reversed by macitentan in rat)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:283407 HCAPLUS Full-text
DOCUMENT NUMBER: 155:112899
TITLE: Macitentan ACT-064992, a tissue-targeting endothelin

receptor antagonist, enhances therapeutic efficacy of paclitaxel by modulating survival pathways in orthotopic models of metastatic human ovarian cancer

AUTHOR(S): Kim, Sun-Jin; Kim, Jang Seong; Kim, Seung Wook; Brantley, Emily; Yun, Seok Joong; He, Junqin; Maya, Marva; Zhang, Fahao; Wu, Qiuyu; Lehembre, Francois; Regenass, Urs; Fidler, Isaiah J.

CORPORATE SOURCE: Department of Cancer Biology, Cancer Metastasis Research Center, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

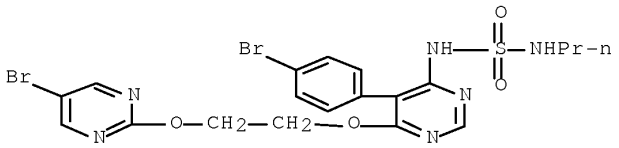
SOURCE: Neoplasia (Ann Arbor, MI, United States) (2011), 13(2), 167-179
CODEN: NEOPFL; ISSN: 1522-8002
URL: http://www.neoplasia.com/pdf/manuscript/v13i02/neo10806.pdf

PUBLISHER: Neoplasia Press Inc.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macitentan (ACT-064992), a tissue-targeting endothelin receptor antagonist, enhances therapeutic efficacy of paclitaxel by modulating survival pathways in orthotopic models of metastatic human ovarian cancer)

RN 441798-33-0 HCAPLUS

CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:203084 HCAPLUS Full-text

DOCUMENT NUMBER: 154:251092

TITLE: Treatment of astrocyte-protected brain metastases using endothelin receptor antagonists in combination with cytotoxic chemotherapy and radiotherapy

INVENTOR(S): Fidler, Isaiah J.; Kim, Sun-Jin

PATENT ASSIGNEE(S): University of Texas System, USA

SOURCE: PCT Int. Appl., 56pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

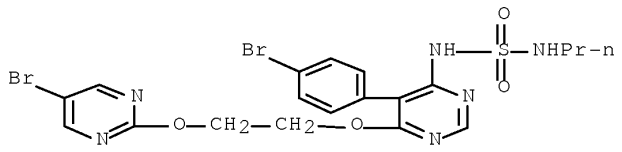
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011019630	A2	20110217	WO 2010-US44832	20100809
WO 2011019630	A3	20110603		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2770397	A1	20110217	CA 2010-2770397	20100809
AU 2010282744	A1	20120322	AU 2010-282744	20100809
CN 102510719	A	20120620	CN 2010-80040990	20100809
EP 2464218	A2	20120620	EP 2010-742690	20100809
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR				
KR 2012088665	A	20120808	KR 2012-7006203	20100809
ZA 2012000980	A	20121031	ZA 2012-980	20120209
US 20120144510	A1	20120607	US 2012-390072	20120210
PRIORITY APPLN. INFO.:			US 2009-232687P P	20090810
			WO 2010-US44832 W	20100809

IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACT-064992; treatment of astrocyte-protected brain metastases using endothelin receptor antagonists in combination with cytotoxic chemotherapy and radiotherapy)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

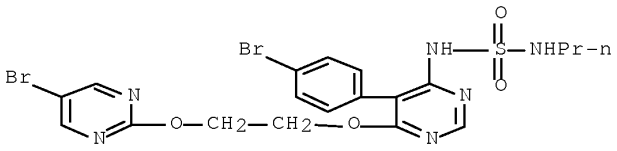


IT 1266239-89-7, Bosentan-macitentan mixt.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of astrocyte-protected brain metastases using endothelin receptor antagonists in combination with cytotoxic chemotherapy and radiotherapy)
RN 1266239-89-7 HCAPLUS
CN Benzenesulfonamide, 4-(1,1-dimethylethyl)-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)[2,2'-bipyrimidin]-4-yl]-, mixt. with N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-

pyrimidinyl]-N'-propylsulfamide (CA INDEX NAME)

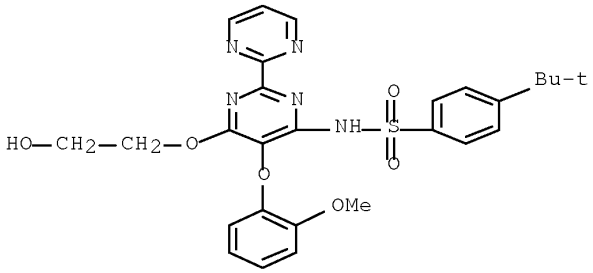
CM 1

CRN 441798-33-0
CMF C19 H20 Br2 N6 O4 S



CM 2

CRN 147536-97-8
CMF C27 H29 N5 O6 S



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L3 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1568833 HCAPLUS Full-text
DOCUMENT NUMBER: 154:56070
TITLE: Sulfonylurea modulators of endothelin receptor
INVENTOR(S): Rao, Tadimeti; Zhang, Chengzhi
PATENT ASSIGNEE(S): Auspex Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 57pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010144477	A2	20101216	WO 2010-US37812	20100608
WO 2010144477	A3	20110421		

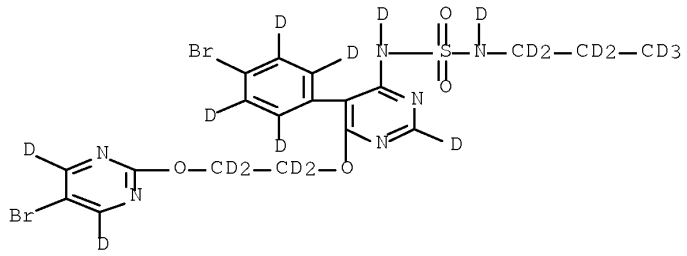
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,

ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE,
SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ,
TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

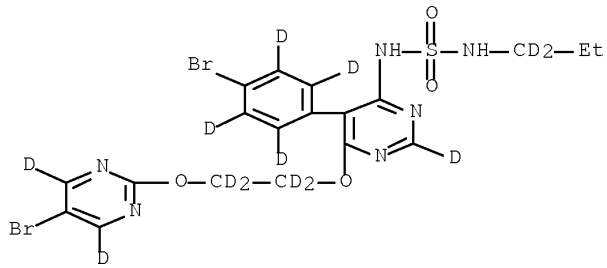
US 20110082151 A1 20110407 US 2010-796527 20100608
PRIORITY APPLN. INFO.: US 2009-186605P P 20090612
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 154:56070

IT 1258427-10-9 1258427-11-0 1258427-12-1
1258427-13-2 1258427-14-3 1258427-15-4
1258427-16-5 1258427-17-6 1258427-18-7
1258427-19-8 1258427-20-1 1258427-21-2
1258427-22-3 1258427-23-4 1258427-24-5
1258427-25-6 1258427-26-7 1258427-27-8
1258427-28-9 1258427-29-0 1258427-30-3
1258427-31-4 1258427-32-5 1258427-33-6
1258427-34-7 1258427-35-8 1258427-36-9
1258427-37-0 1258427-38-1 1258427-39-2
1258427-40-5 1258427-41-6 1258427-42-7
1258427-43-8 1258427-44-9 1258427-45-0
1258427-46-1 1258427-47-2 1258427-48-3
1258427-49-4 1258427-50-7 1258427-51-8
1258427-52-9 1258427-53-0 1258427-54-1
1258427-55-2 1258427-56-3 1258427-57-4
1258427-58-5 1258427-59-6 1258427-60-9
1258427-61-0 1258427-62-1 1258427-64-3
1258427-65-4 1258427-66-5 1258427-67-6
1258427-69-8 1258427-72-3 1258427-74-5
1258427-76-7 1258427-77-8 1258427-79-0
1258427-80-3 1258427-81-4 1258427-82-5
1258427-83-6 1258427-84-7 1258427-85-8
1258427-86-9 1258427-87-0 1258427-88-1
1258427-89-2 1258427-90-5 1258427-91-6
1258427-92-7 1258427-93-8 1258427-94-9
1258427-95-0 1258427-96-1 1258427-97-2
1258427-98-3 1258427-99-4 1258428-00-0
1258428-01-1 1258428-02-2 1258428-03-3
1258428-04-4 1258428-05-5 1258428-06-6
1258428-07-7 1258428-08-8 1258428-09-9
1258428-10-2 1258428-11-3 1258428-13-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulfonylurea modulators of endothelin receptor for disease treatment and combination with other agents in relation to decreased metabolism and hepatotoxicity)

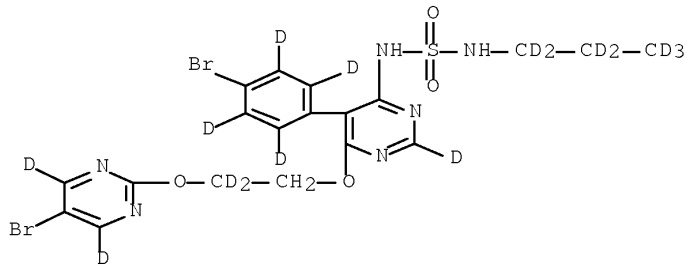
RN 1258427-10-9 HCAPLUS
CN Sulfamide-N,N'-d2, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



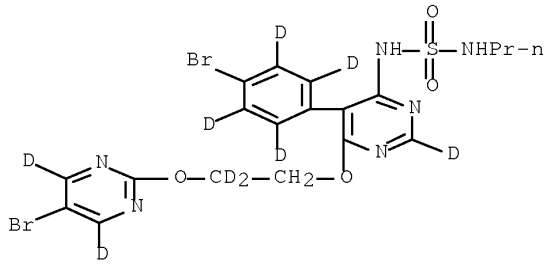
RN 1258427-11-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



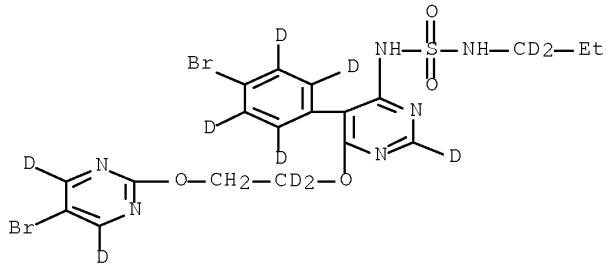
RN 1258427-12-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



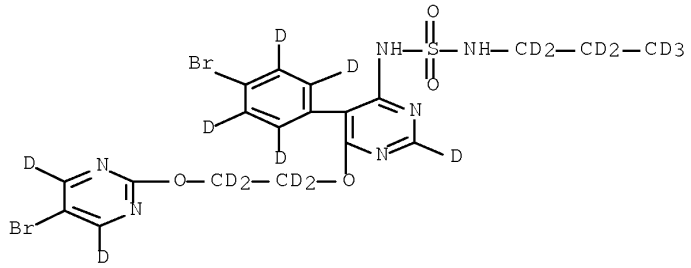
RN 1258427-13-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



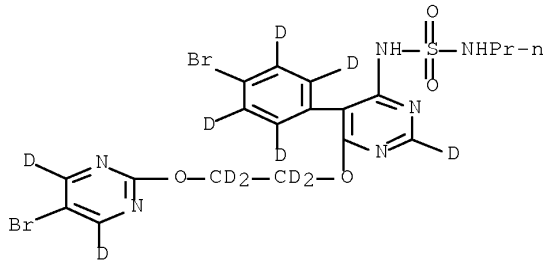
RN 1258427-14-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



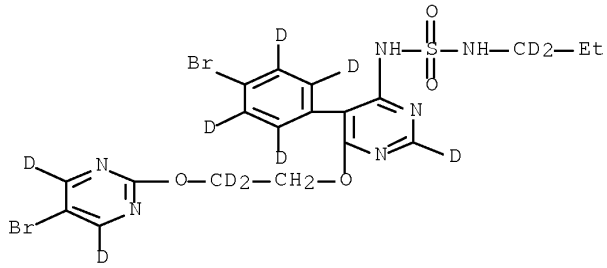
RN 1258427-15-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



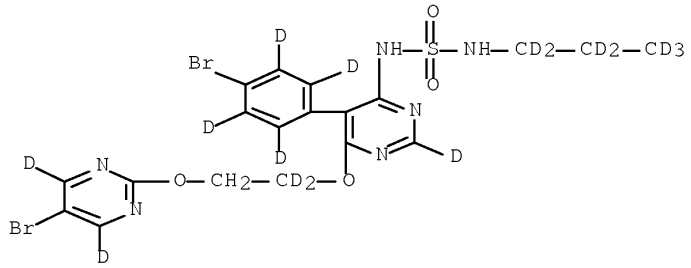
RN 1258427-16-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



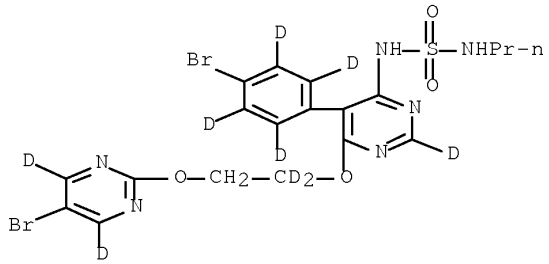
RN 1258427-17-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



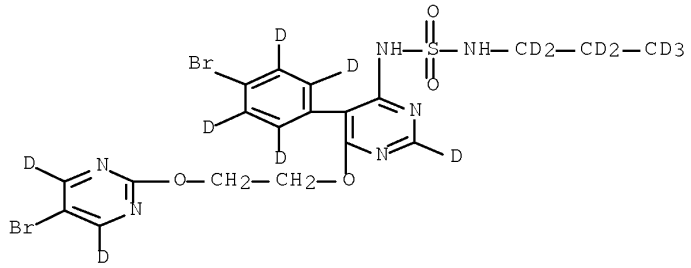
RN 1258427-18-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



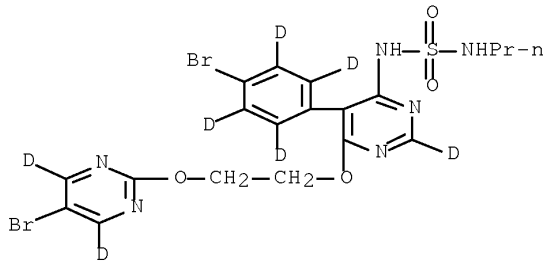
RN 1258427-19-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



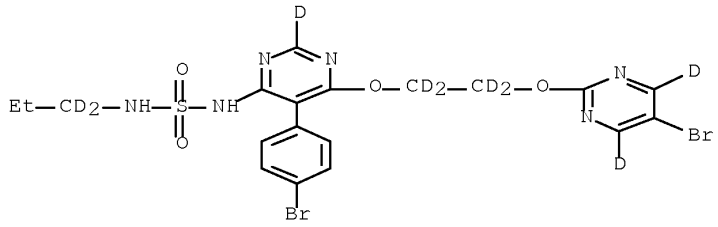
RN 1258427-20-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



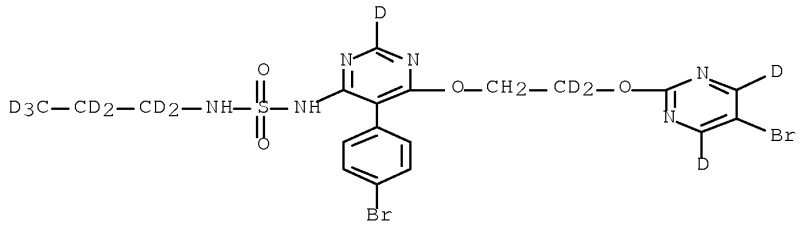
RN 1258427-21-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



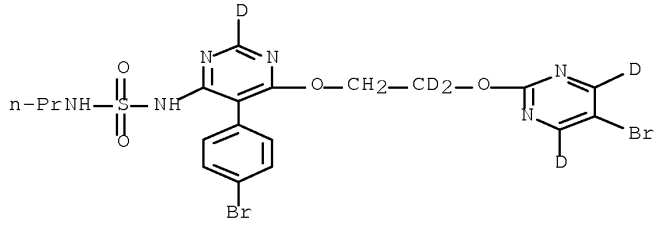
RN 1258427-22-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



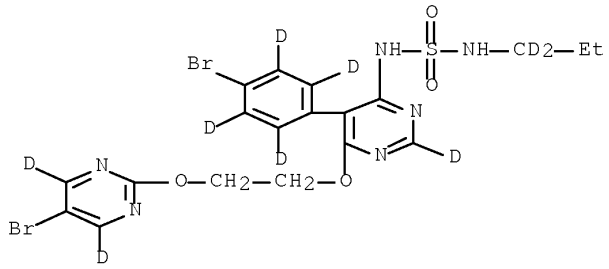
RN 1258427-23-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



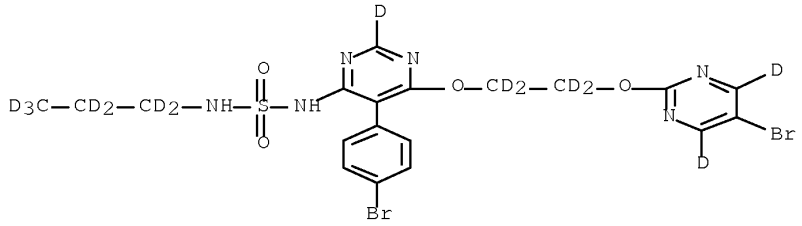
RN 1258427-24-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



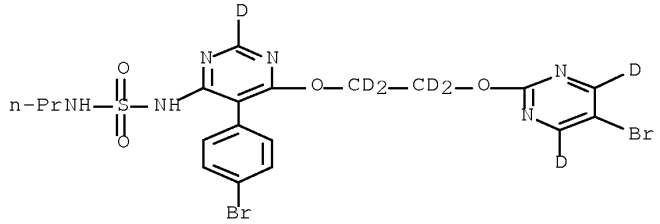
RN 1258427-25-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



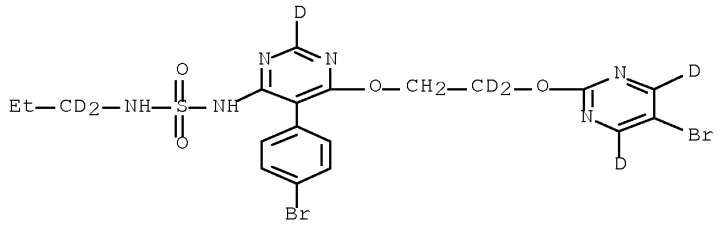
RN 1258427-26-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



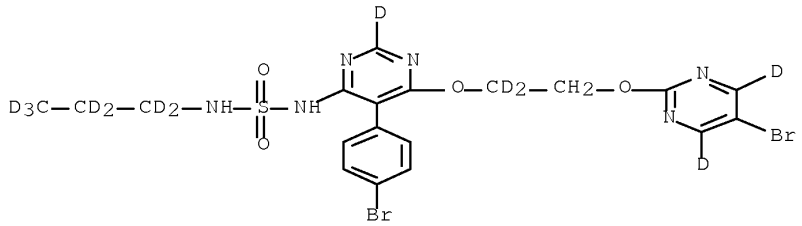
RN 1258427-27-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



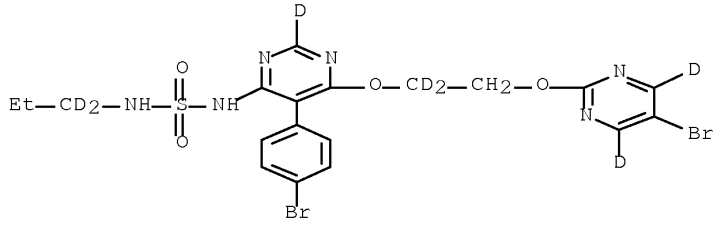
RN 1258427-28-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



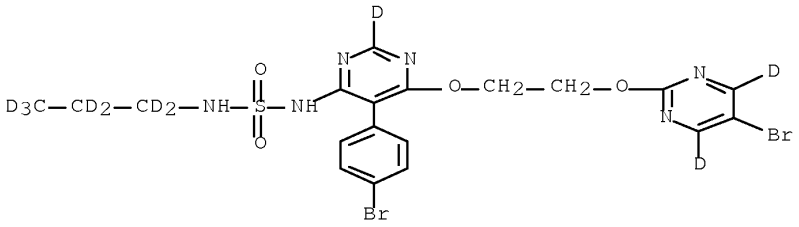
RN 1258427-29-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



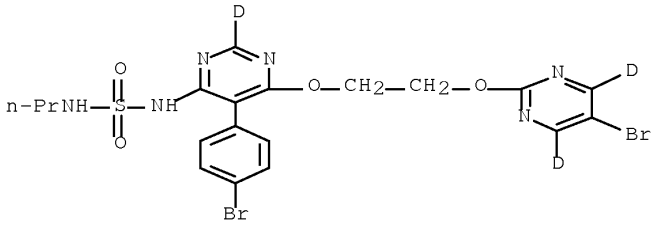
RN 1258427-30-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



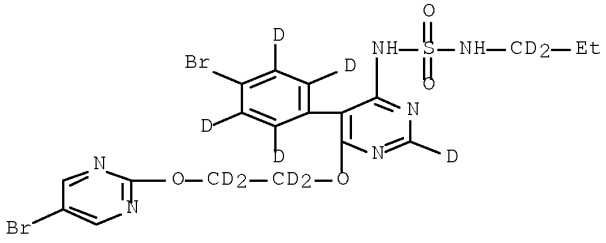
RN 1258427-31-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



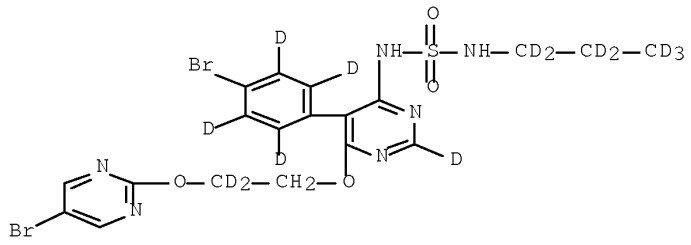
RN 1258427-32-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



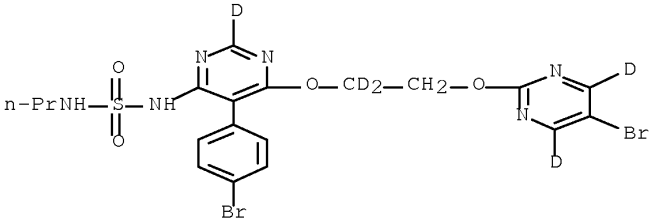
RN 1258427-33-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



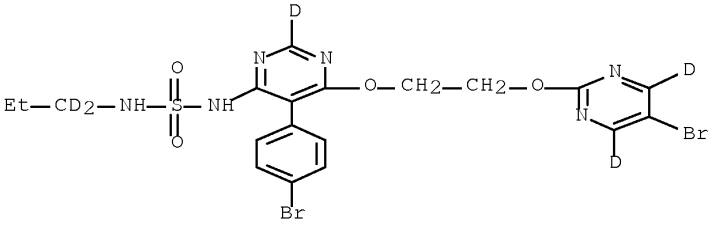
RN 1258427-34-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



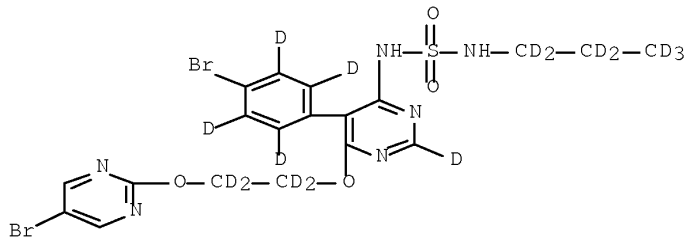
RN 1258427-35-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



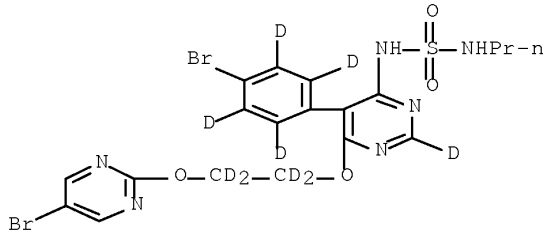
RN 1258427-36-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



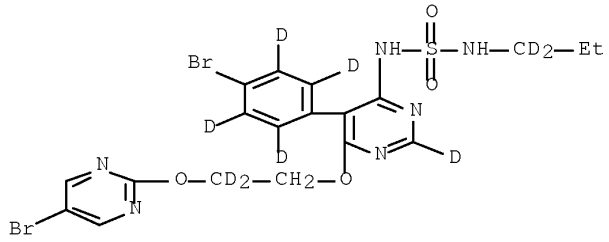
RN 1258427-37-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



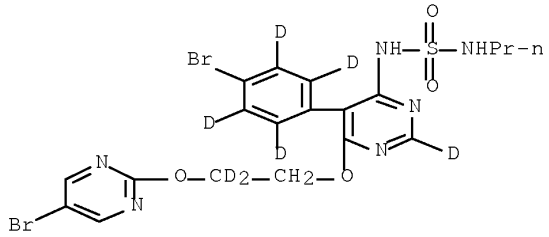
RN 1258427-38-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



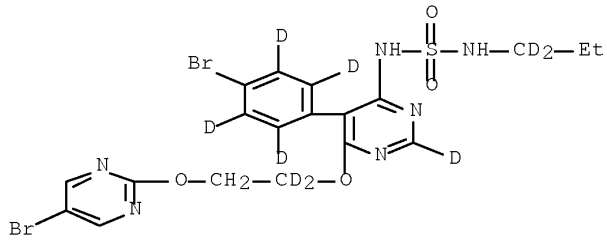
RN 1258427-39-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



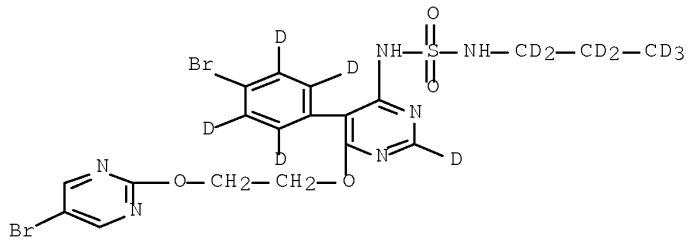
RN 1258427-40-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



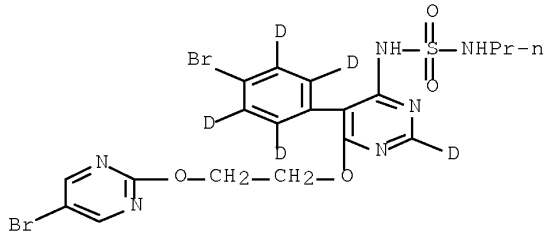
RN 1258427-41-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



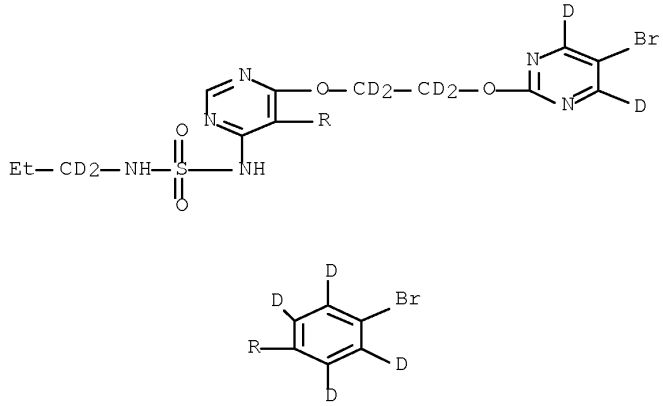
RN 1258427-42-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



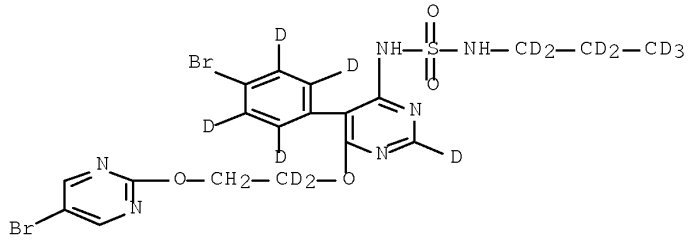
RN 1258427-43-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



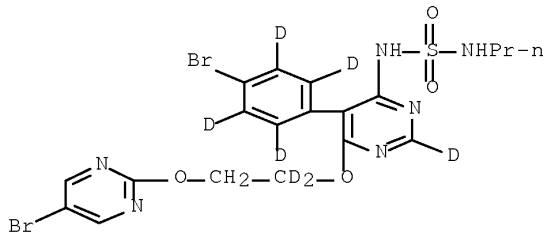
RN 1258427-44-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



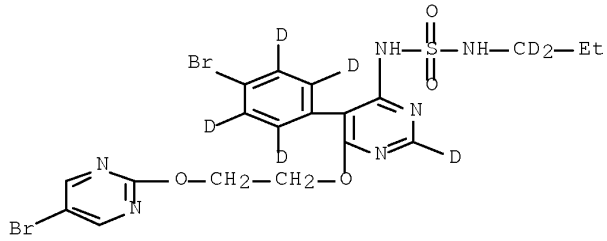
RN 1258427-45-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



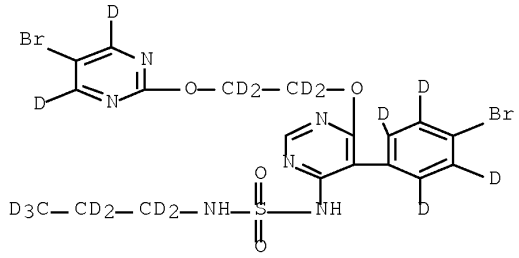
RN 1258427-46-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



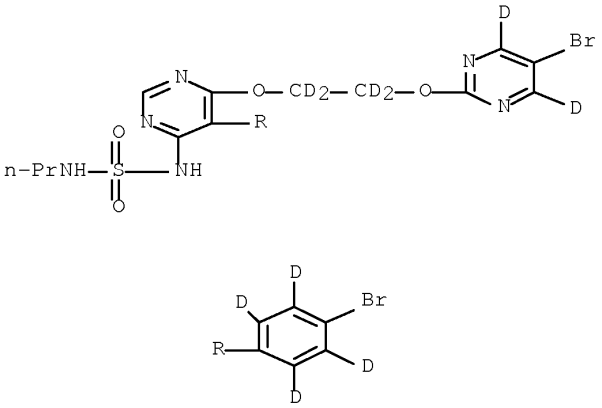
RN 1258427-47-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



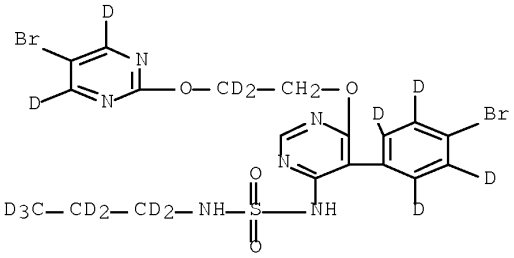
RN 1258427-48-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



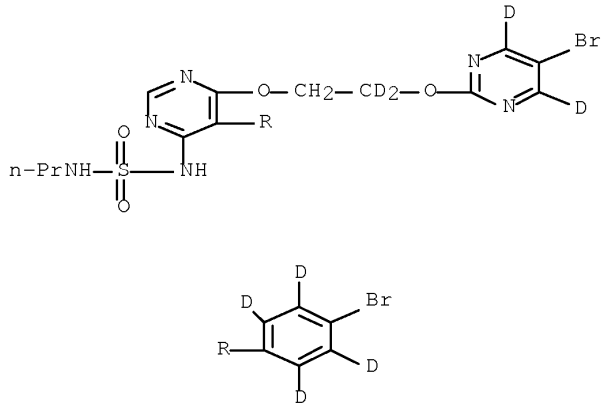
RN 1258427-49-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



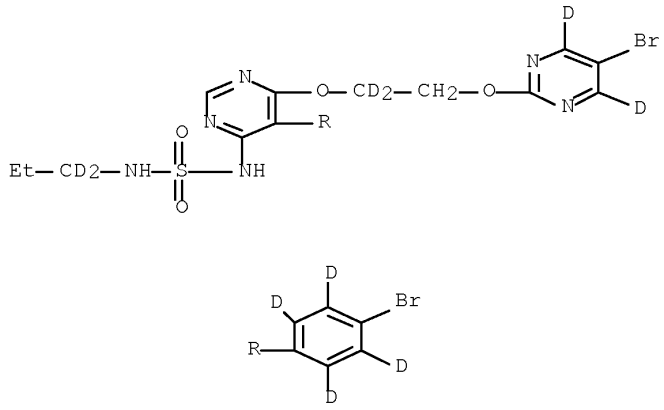
RN 1258427-50-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



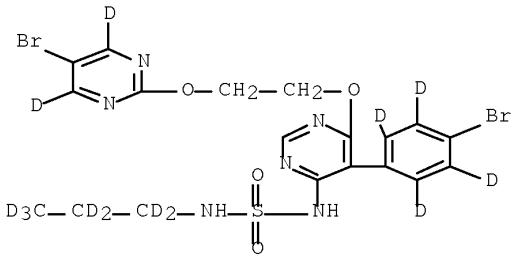
RN 1258427-51-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



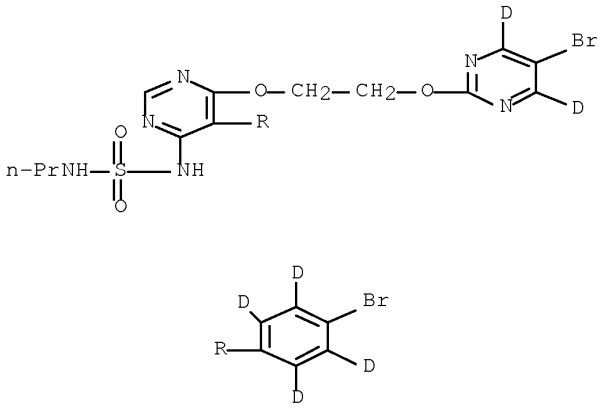
RN 1258427-52-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



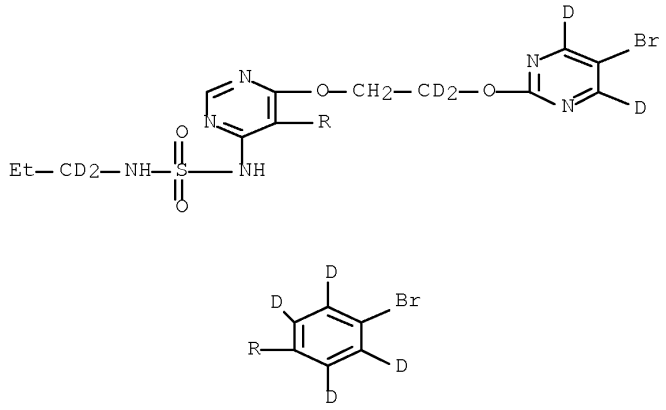
RN 1258427-53-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



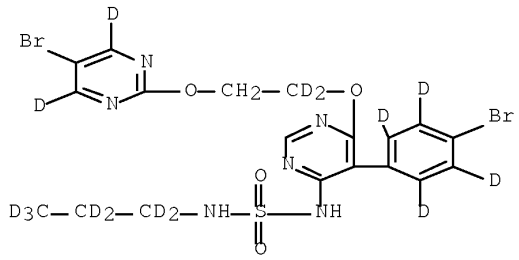
RN 1258427-54-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



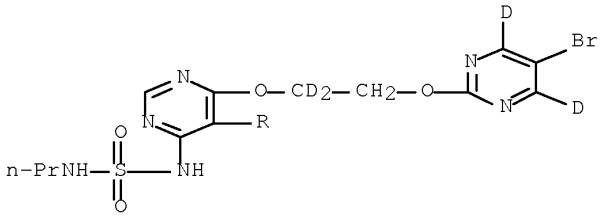
RN 1258427-55-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

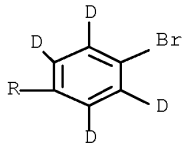


RN 1258427-56-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)

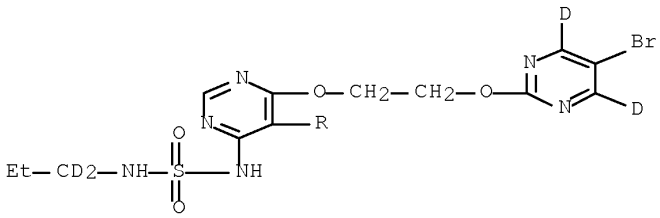


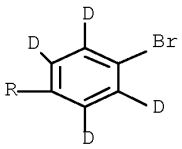
RN 1258427-57-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



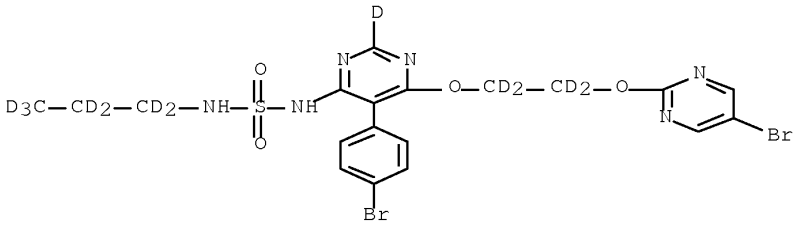


RN 1258427-58-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

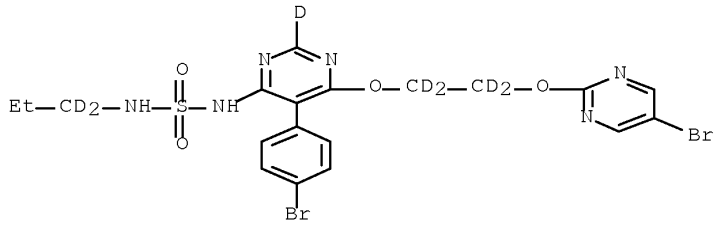




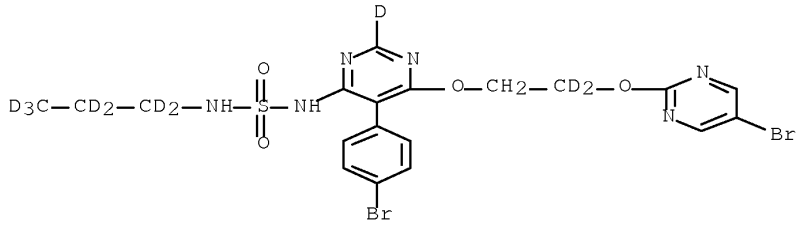
RN 1258427-59-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



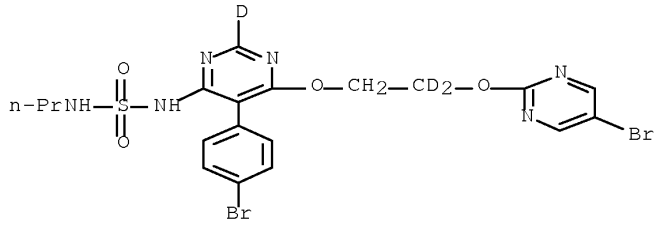
RN 1258427-60-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



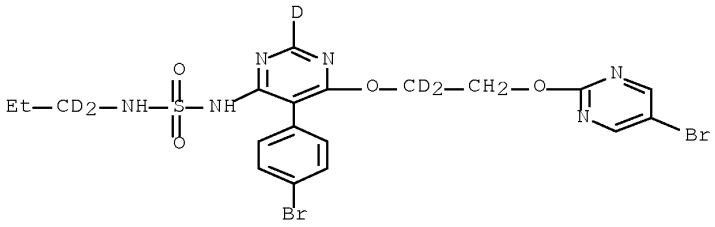
RN 1258427-61-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



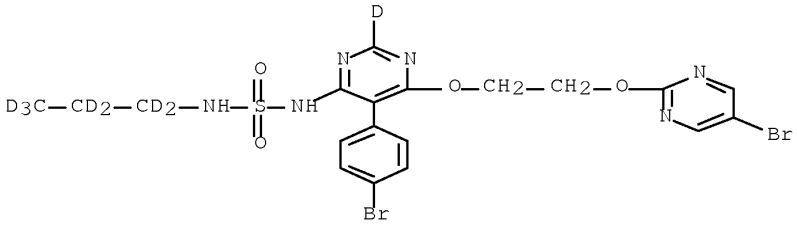
RN 1258427-62-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



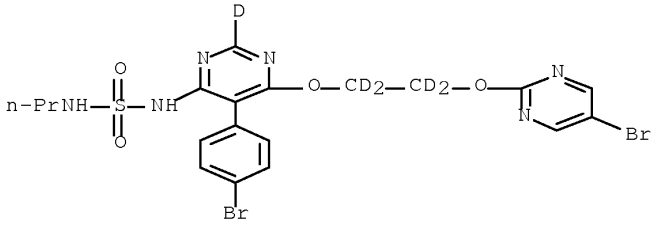
RN 1258427-64-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



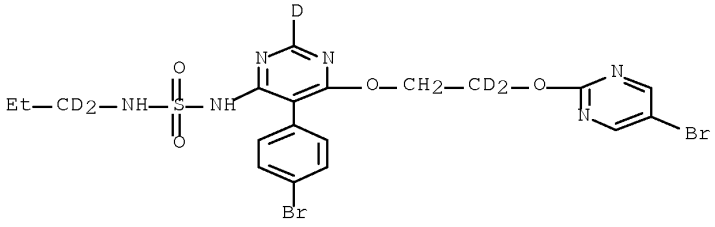
RN 1258427-65-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



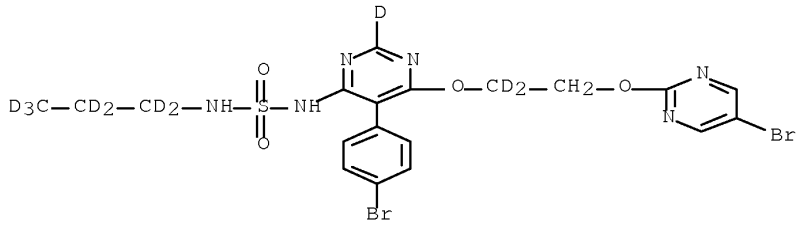
RN 1258427-66-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



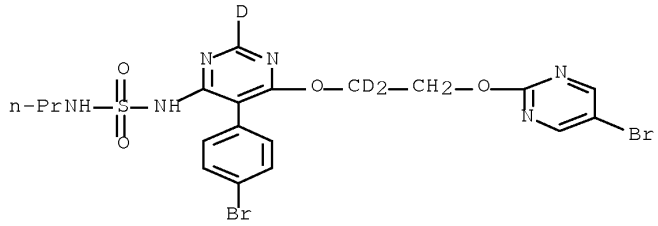
RN 1258427-67-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



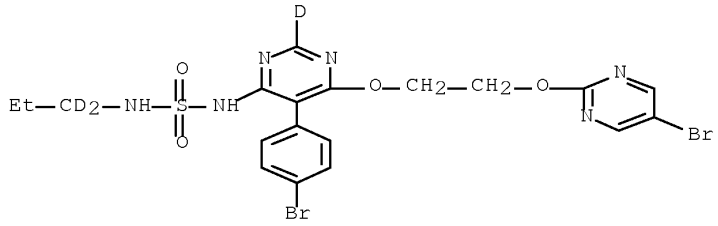
RN 1258427-69-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



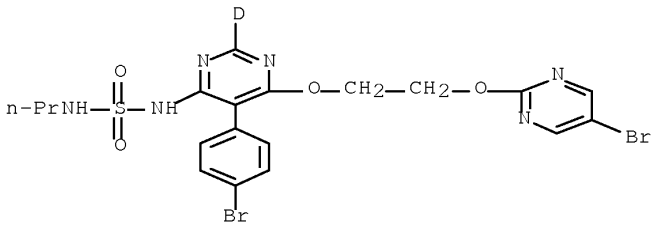
RN 1258427-72-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



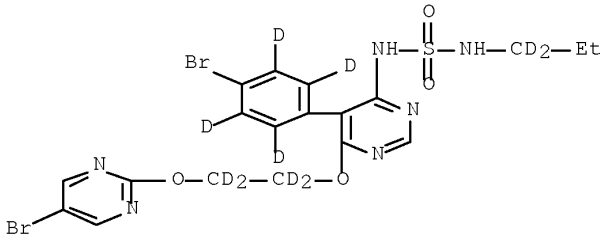
RN 1258427-74-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



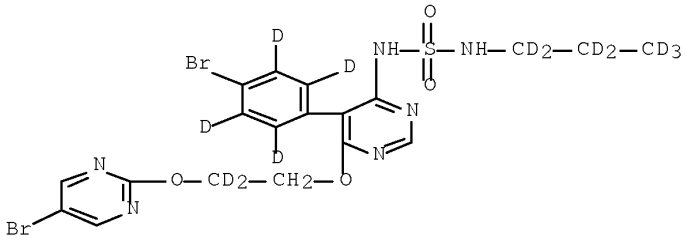
RN 1258427-76-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl-2-d]-N'-propyl- (CA INDEX NAME)



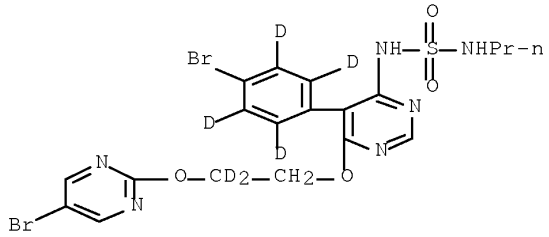
RN 1258427-77-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



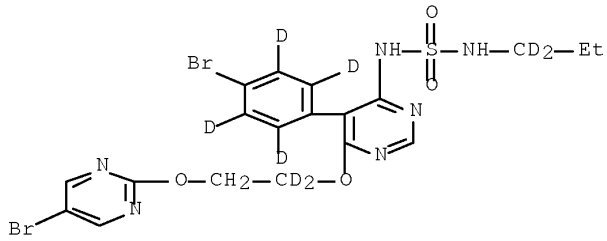
RN 1258427-79-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



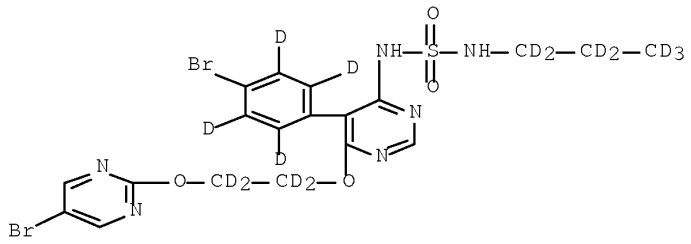
RN 1258427-80-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



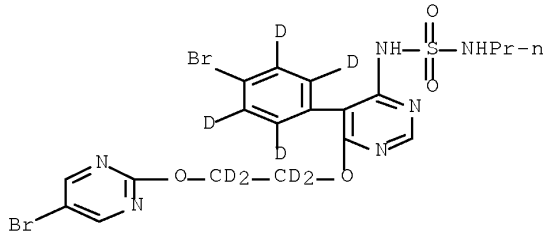
RN 1258427-81-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



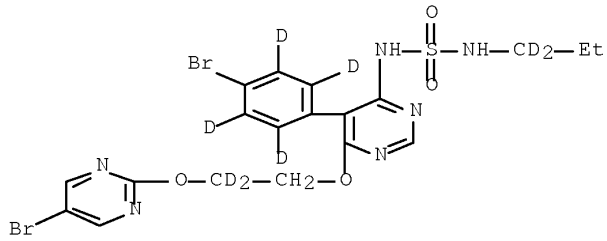
RN 1258427-82-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



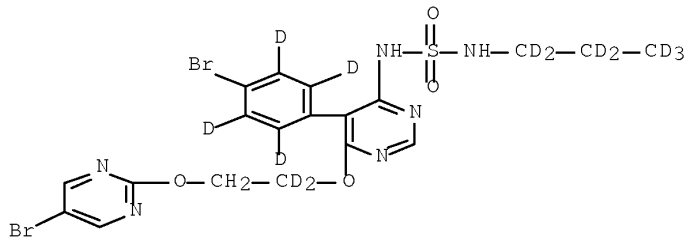
RN 1258427-83-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



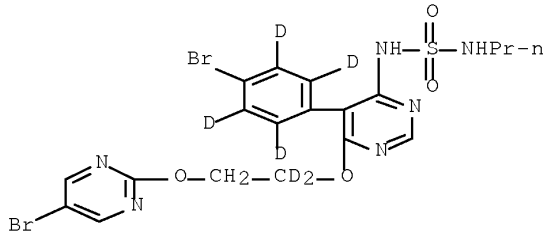
RN 1258427-84-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



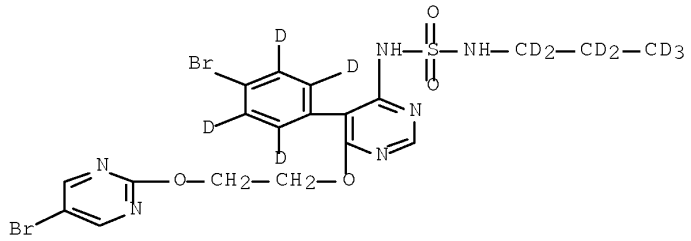
RN 1258427-85-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



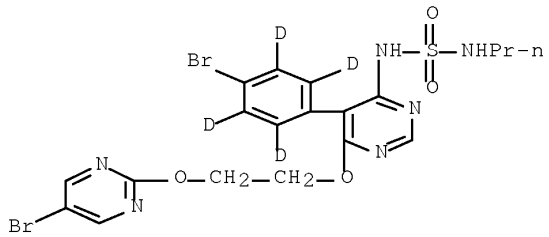
RN 1258427-86-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



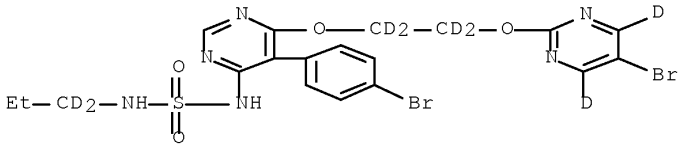
RN 1258427-87-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



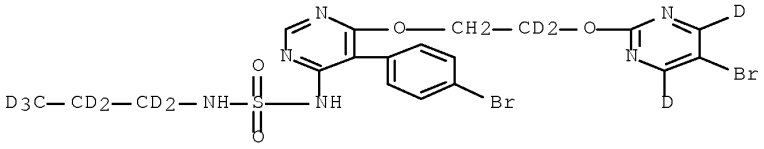
RN 1258427-88-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



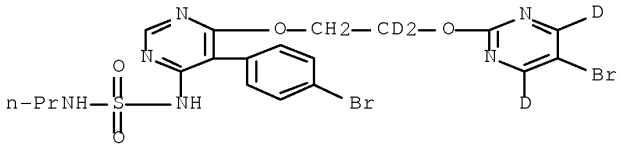
RN 1258427-89-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



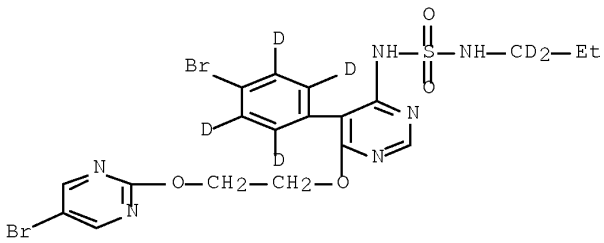
RN 1258427-90-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



RN 1258427-91-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

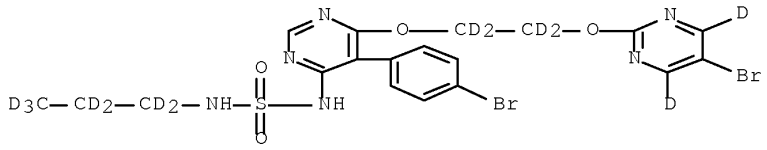


RN 1258427-92-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl-2,3,5,6-d4)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

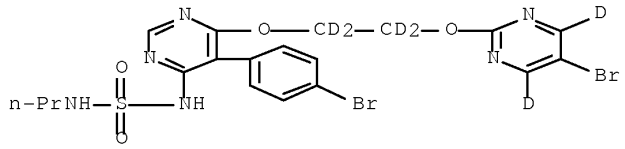


RN 1258427-93-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-

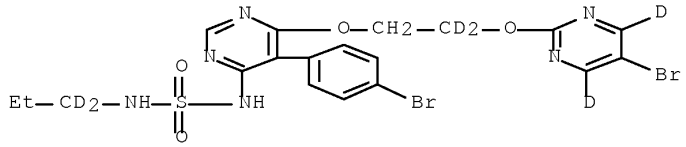
d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)-
(CA INDEX NAME)



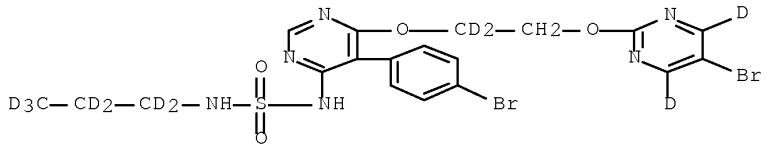
RN 1258427-94-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-
d2)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



RN 1258427-95-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-
d2)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

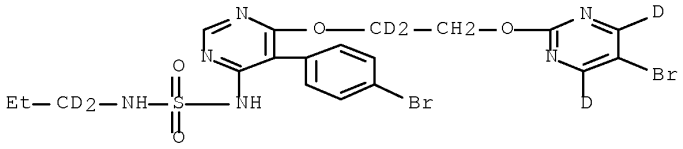


RN 1258427-96-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-
d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA
INDEX NAME)

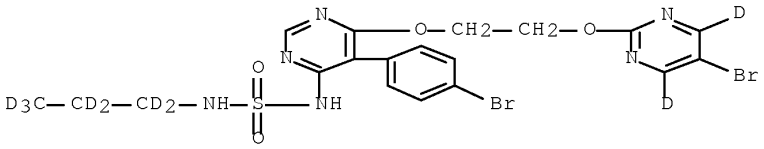


RN 1258427-97-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-

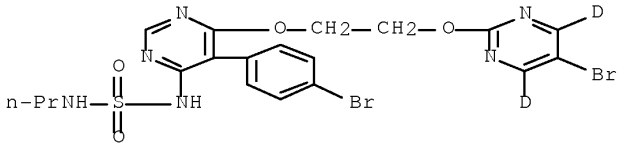
d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



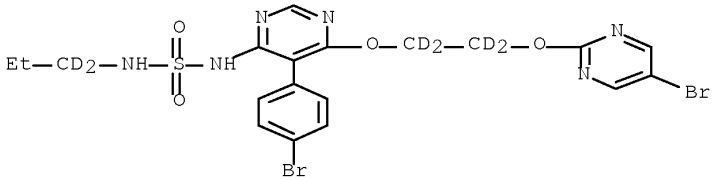
RN 1258427-98-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



RN 1258427-99-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

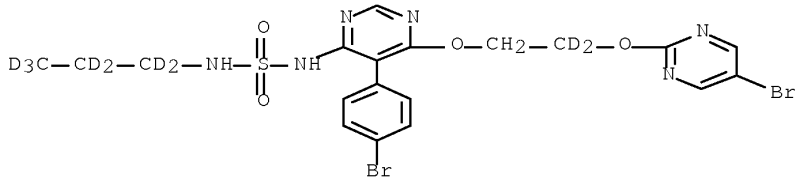


RN 1258428-00-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

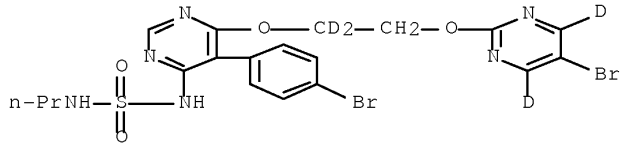


RN 1258428-01-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-

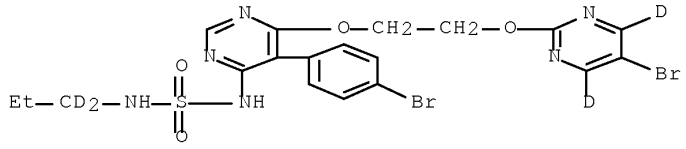
2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



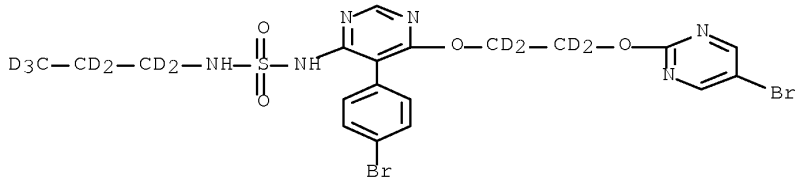
RN 1258428-02-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



RN 1258428-03-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl-4,6-d2)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)

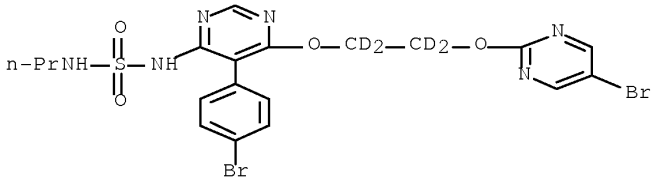


RN 1258428-04-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1,2,2-d4]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)

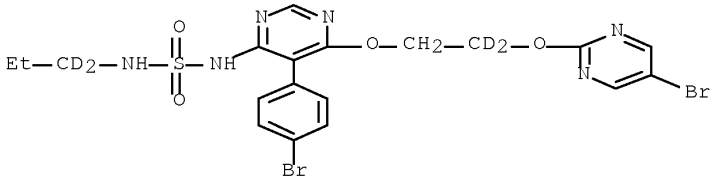


RN 1258428-05-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-

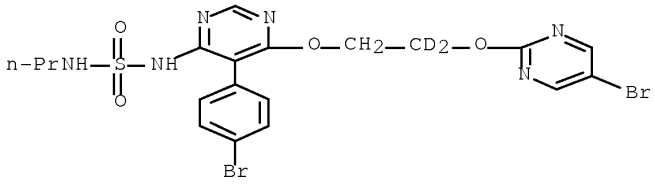
1,1,2,2-d4]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



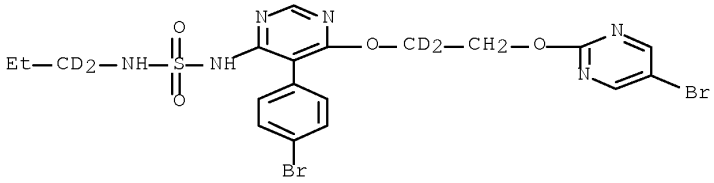
RN 1258428-06-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



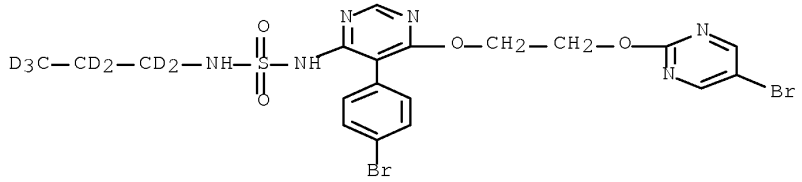
RN 1258428-07-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-2,2-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



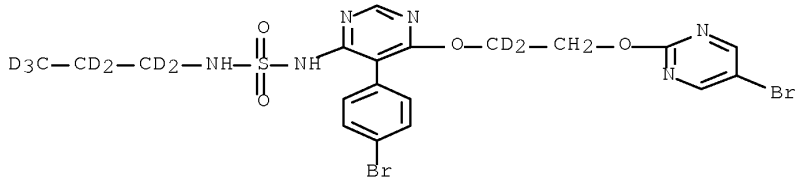
RN 1258428-08-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



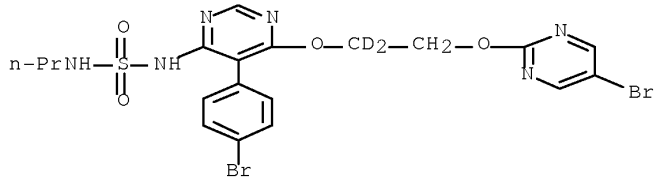
RN 1258428-09-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



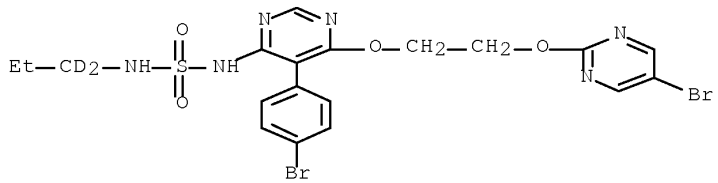
RN 1258428-10-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-(propyl-1,1,2,2,3,3,3-d7)- (CA INDEX NAME)



RN 1258428-11-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy-1,1-d2]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

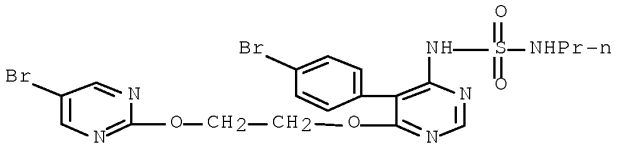


RN 1258428-13-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(propyl-1,1-d2)- (CA INDEX NAME)



L3 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1327581 HCAPLUS Full-text
DOCUMENT NUMBER: 155:111760
TITLE: Macitentan, a tissue-targeting endothelin receptor antagonist for the potential oral treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis
AUTHOR(S): Raja, Shahzad G.
CORPORATE SOURCE: Department of Cardiothoracic Surgery, Royal Brompton & Harefield NHS Trust, Harefield Hospital, Harefield, London, UB9 6JH, UK
SOURCE: Current Opinion in Investigational Drugs (BioMed Central) (2010), 11(9), 1066-1073
CODEN: COIDAZ; ISSN: 2040-3429
URL: http://www.biomedcentral.com/content/pdf/cd-1125271.pdf

PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potential role of macitentan, a tissue-targeting endothelin receptor antagonist for the treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

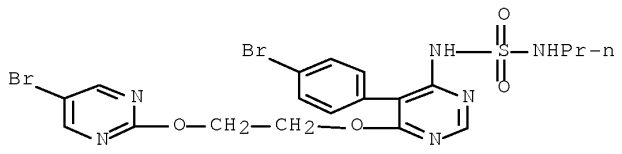
L3 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:214047 HCAPLUS Full-text
DOCUMENT NUMBER: 152:271363
TITLE: Therapeutic compositions containing macitentan and prostacyclin receptor agonists
INVENTOR(S): Clozel, Martine
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.
SOURCE: PCT Int. Appl., 13pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

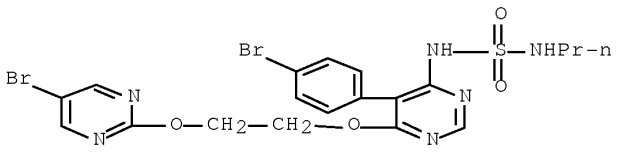
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010018549	A2	20100218	WO 2009-IB53553	20090812
WO 2010018549	A3	20100729		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2009280843	A1	20100218	AU 2009-280843	20090812
CA 2731370	A1	20100218	CA 2009-2731370	20090812
AR 73031	A1	20101006	AR 2009-103113	20090812
KR 2011045006	A	20110503	KR 2011-7003547	20090812
EP 2315587	A2	20110504	EP 2009-786912	20090812
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS				
CN 102099026	A	20110615	CN 2009-80127993	20090812
CN 102099026	B	20120829		
JP 2011530581	T	20111222	JP 2011-522608	20090812
MX 2011001625	A	20110329	MX 2011-1625	20110211
US 20110136818	A1	20110609	US 2011-58639	20110211
IN 2011CN01623	A	20111202	IN 2011-CN1623	20110308
ZA 2011001900	A	20120829	ZA 2011-1900	20110311

PRIORITY APPLN. INFO.:		WO 2008-IB53252	A	20080813
		WO 2009-IB53553	W	20090812

IT 441798-33-0, Macitentan 441798-33-0D, Macitentan, salts
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. containing macitentan and prostacyclin receptor agonists)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



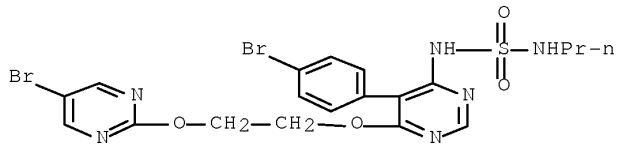
L3 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:21877 HCAPLUS Full-text
DOCUMENT NUMBER: 152:129500
TITLE: Stable pharmaceutical compositions comprising a pyrimidine-sulfamide derivative for treatment of pulmonary hypertension
INVENTOR(S): Adesuyi, Charles Tokunbo; Holman, Lovelace; Lambert, Olivier; Lithgow, Bruce Hamilton
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd., Switz.
SOURCE: U.S. Pat. Appl. Publ., 23pp., Cont.-in-part of U.S. Ser. No. 66,448.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20100004274	A1	20100107	US 2009-388142	20090218
WO 2007031933	A2	20070322	WO 2006-IB53210	20060911
WO 2007031933	A3	20071018		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 2292209	A2	20110309	EP 2010-9910	20060911
EP 2292209	A3	20110504		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
US 20080233188	A1	20080925	US 2008-66448	20080319
JP 2009235073	A	20091015	JP 2009-112258	20090501
JP 5054061	B2	20121024		

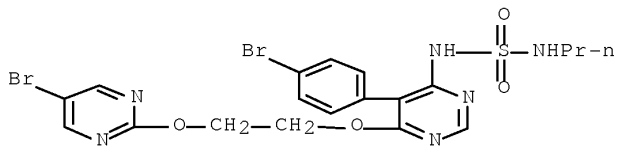
PRIORITY APPLN. INFO.:

WO 2005-EP9775	A	20050912
WO 2006-IB53210	W	20060911
US 2008-66448	A2	20080319
EP 2006-809280	A3	20060911
JP 2008-529767	A3	20060911

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IT 441798-33-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable compns. comprising pyrimidine-sulfamide derivative for treatment of pulmonary hypertension)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



L3 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1284927 HCAPLUS Full-text
DOCUMENT NUMBER: 152:82487
TITLE: Comparison of the dissolution and pharmacokinetic profiles of two galenical formulations of the endothelin receptor antagonist macitentan
AUTHOR(S): Kummer, Oliver; Haschke, Manuel; Hammann, Felix; Bodmer, Michael; Bruderer, Shirin; Regnault, Yann; Dingemanse, Jasper; Kraehenbuehl, Stephan
CORPORATE SOURCE: Division of Clinical Pharmacology & Toxicology and Department of Biomedicine, University Hospital, Basel, CH-4031, Switz.
SOURCE: European Journal of Pharmaceutical Sciences (2009), 38(4), 384-388
CODEN: EPSCED; ISSN: 0928-0987
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dissoln. and pharmacokinetic profiles of two galenical formulations of endothelin receptor antagonist macitentan)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



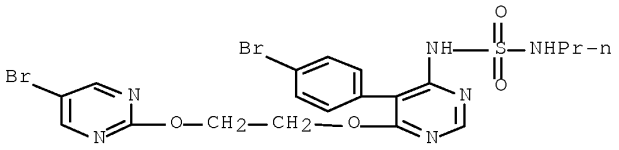
OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1049863 HCAPLUS Full-text
DOCUMENT NUMBER: 151:322310
TITLE: Endothelin receptor antagonist in combination with paclitaxel for treating ovarian cancer
INVENTOR(S): Clozel, Martine; Regenass, Urs
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.
SOURCE: PCT Int. Appl., 16pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009104149	A1	20090827	WO 2009-IB50677	20090219
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2009215329	A1	20090827	AU 2009-215329	20090219
CA 2714608	A1	20090827	CA 2009-2714608	20090219
EP 2254570	A1	20101201	EP 2009-712334	20090219
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS				
KR 2010132489	A	20101217	KR 2010-7018516	20090219
CN 101939001	A	20110105	CN 2009-80104258	20090219
CN 101939001	B	20120620		
JP 2011512399	T	20110421	JP 2010-547291	20090219
AR 70456	A1	20100407	AR 2009-100596	20090220
MX 2010008994	A	20100907	MX 2010-8994	20100816
US 20100311774	A1	20101209	US 2010-867939	20100817
IN 2010CN05776	A	20110415	IN 2010-CN5776	20100915
PRIORITY APPLN. INFO.:			WO 2008-IB50607 A	20080220
			WO 2009-IB50677 W	20090219

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IT 441798-33-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelin receptor antagonist in combination with paclitaxel for treating ovarian cancer)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



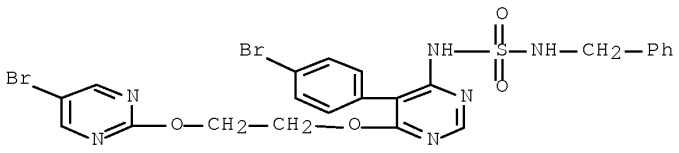
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:239548 HCAPLUS Full-text
DOCUMENT NUMBER: 150:260215
TITLE: Preparation of 4-pyrimidinesulfamide derivatives as endothelin receptor antagonists
INVENTOR(S): Bolli, Martin; Boss, Christoph; Treiber, Alexander
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009024906	A1	20090226	WO 2008-IB53282	20080815
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AR 70018	A1	20100310	AR 2008-103552	20080814
AU 2008290234	A1	20090226	AU 2008-290234	20080815
CA 2695511	A1	20090226	CA 2008-2695511	20080815
KR 2010052517	A	20100519	KR 2010-7004945	20080815
EP 2190837	A1	20100602	EP 2008-807330	20080815
EP 2190837	B1	20120815		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS				
JP 2010536742	T	20101202	JP 2010-520674	20080815
NZ 583990	A	20120629	NZ 2008-583990	20080815
PT 2190837	E	20121031	PT 2008-807330	20080815
IL 203936	A	20121129	IL 2008-203936	20080815
CN 101772494	A	20100707	CN 2008-80101679	20100202
US 20120142716	A1	20120607	US 2010-673413	20100212
US 8324232	B2	20121204		

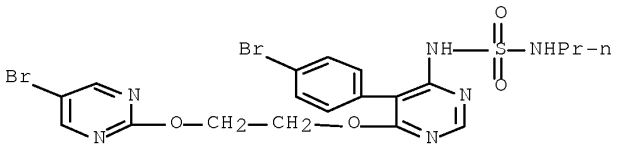
MX 2010001837	A	20100310	MX 2010-1837		20100216
IN 2010CN01417	A	20100813	IN 2010-CN1417		20100312
ZA 2010001872	A	20110525	ZA 2010-1872		20100316
PRIORITY APPLN. INFO.:			WO 2007-IB53292	A	20070817
			WO 2008-IB52571	A	20080626
			WO 2008-IB53282	W	20080815

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 150:260215
IT 441796-09-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-pyrimidinesulfamide derivs. as endothelin receptor antagonists useful in treatment and prevention of endothelin - mediated diseases)
RN 441796-09-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1440652 HCAPLUS Full-text
DOCUMENT NUMBER: 150:136402
TITLE: Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist
AUTHOR(S): Iglarz, Marc; Binkert, Christoph; Morrison, Keith; Fischli, Walter; Gatfield, John; Treiber, Alexander; Weller, Thomas; Bolli, Martin H.; Boss, Christoph; Buchmann, Stephan; Capeleto, Bruno; Hess, Patrick; Qiu, Changbin; Clozel, Martine
CORPORATE SOURCE: Drug Discovery Department, Actelion Pharmaceuticals Ltd., Allschwil, Switz.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2008), 327(3), 736-745
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 441798-33-0, Macitentan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of macitentan (Actelion-1 or ACT-064992), an orally active tissue-targeting dual endothelin receptor antagonist)
RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 34 THERE ARE 34 CAPLUS RECORDS THAT CITE THIS RECORD (34 CITINGS)
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:289587 HCAPLUS Full-text
DOCUMENT NUMBER: 148:299909
TITLE: PDE5 inhibitor compositions for treatment of diseases involving vasoconstriction
INVENTOR(S): Clozel, Martine
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd., Switz.
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008026156	A2	20080306	WO 2007-IB53448	20070828
WO 2008026156	A3	20081016		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AR 62501	A1	20081112	AR 2007-103749	20070823
AU 2007290099	A1	20080306	AU 2007-290099	20070828
CA 2659770	A1	20080306	CA 2007-2659770	20070828
EP 2059246	A2	20090520	EP 2007-826167	20070828
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
CN 101511365	A	20090819	CN 2007-80032148	20070828
CN 101511365	B	20110817		
JP 2010502588	T	20100128	JP 2009-526239	20070828
NZ 575702	A	20111125	NZ 2007-575702	20070828
RU 2462249	C2	20120927	RU 2009-111378	20070828
IL 197235	A	20121031	IL 2007-197235	20070828
MX 2009002057	A	20090306	MX 2009-2057	20090224

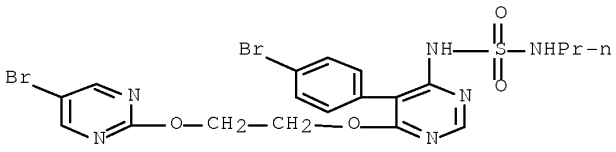
US 20090318459	A1	20091224	US 2009-439290		20090227
US 8268847	B2	20120918			
KR 2009057009	A	20090603	KR 2009-7005029		20090311
NO 2009001254	A	20090326	NO 2009-1254		20090326
ZA 2009002164	A	20100630	ZA 2009-2164		20090327
HK 1133597	A1	20120525	HK 2010-101538		20100211
PRIORITY APPLN. INFO.:			WO 2006-IB52999	A	20060829
			WO 2006-IB53857	A	20061019
			WO 2007-IB53448	W	20070828

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 441798-33-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PDE5 inhibitor compns. for treatment of diseases involving vasoconstriction)

RN 441798-33-0 HCAPLUS

CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



L3 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2007:330339 HCAPLUS Full-text

DOCUMENT NUMBER: 146:344368

TITLE: Stable pharmaceutical composition comprising a pyrimidine-sulfamide

INVENTOR(S): Adesuyi, Charles Tokunbo; Holman, Lovelace; Lambert, Olivier; Lithgow, Bruce Hamilton

PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.

SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007031933	A2	20070322	WO 2006-IB53210	20060911
WO 2007031933	A3	20071018		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

AU	2006290309	A1	20070322	AU 2006-290309	20060911
AU	2006290309	B2	20120405		
CA	2621273	A1	20070322	CA 2006-2621273	20060911
EP	1928409	A2	20080611	EP 2006-809280	20060911
EP	1928409	B1	20120912		
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR				
CN	101262847	A	20080910	CN 2006-80033375	20060911
CN	101262847	B	20101124		
JP	2009519893	T	20090521	JP 2008-529767	20060911
JP	4955685	B2	20120620		
EP	2292209	A2	20110309	EP 2010-9910	20060911
EP	2292209	A3	20110504		
	R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
NZ	567188	A	20110429	NZ 2006-567188	20060911
BR	2006015898	A2	20110531	BR 2006-15898	20060911
RU	2424805	C2	20110727	RU 2008-113869	20060911
IL	190072	A	20120924	IL 2006-190072	20060911
TW	323661	B	20100421	TW 2006-133695	20060912
MX	2008003370	A	20080523	MX 2008-3370	20080310
US	20080233188	A1	20080925	US 2008-66448	20080319
ZA	2008002947	A	20091230	ZA 2008-2947	20080403
KR	2008055897	A	20080619	KR 2008-7008450	20080408
NO	2008001724	A	20080409	NO 2008-1724	20080409
IN	2008CN01806	A	20090605	IN 2008-CN1806	20080410
US	20100004274	A1	20100107	US 2009-388142	20090218
HK	1121950	A1	20110527	HK 2009-102261	20090309
JP	2009235073	A	20091015	JP 2009-112258	20090501
JP	5054061	B2	20121024		

PRIORITY APPLN. INFO.:	WO 2005-EP9775	A	20050912
	EP 2006-809280	A3	20060911
	JP 2008-529767	A3	20060911
	WO 2006-IB53210	W	20060911
	US 2008-66448	A2	20080319

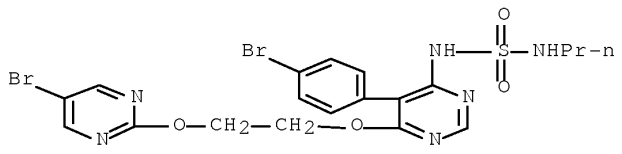
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 441798-33-0

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable pharmaceutical composition comprising pyrimidine-sulfamide)

RN 441798-33-0 HCAPLUS

CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

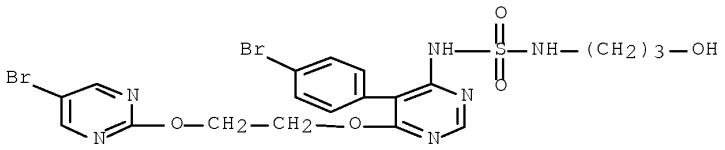
L3 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2006:471809 HCAPLUS Full-text
DOCUMENT NUMBER: 144:488674
TITLE: Preparation of novel pyrimidine-sulfamides as endothelin receptor antagonists
INVENTOR(S): Boss, Christoph; Fischli, Walter; Weller, Thomas; Clozel, Martine; Bolli, Martin
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006051502	A2	20060518	WO 2005-IB53716	20051111
WO 2006051502	A3	20060908		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005303435	A1	20060518	AU 2005-303435	20051111
CA 2586106	A1	20060518	CA 2005-2586106	20051111
AR 51764	A1	20070207	AR 2005-104726	20051111
EP 1833821	A2	20070919	EP 2005-802290	20051111
EP 1833821	B1	20110330		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 101056872	A	20071017	CN 2005-80038466	20051111
JP 2008519826	T	20080612	JP 2007-540808	20051111
JP 5020089	B2	20120905		
BR 2005017565	A	20081014	BR 2005-17565	20051111
AT 503752	T	20110415	AT 2005-802290	20051111
PT 1833821	E	20110606	PT 2005-802290	20051111
ES 2362103	T3	20110628	ES 2005-802290	20051111
MX 2007005566	A	20070521	MX 2007-5566	20070509
US 20080004298	A1	20080103	US 2007-718922	20070509
US 7868012	B2	20110111		
KR 2007085787	A	20070827	KR 2007-7012690	20070605

PRIORITY APPLN. INFO.:		WO 2004-EP12774 A	20041111
		WO 2005-IB53716 W	20051111

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 144:488674; MARPAT 144:488674
IT 887366-70-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of novel pyrimidine-sulfamides as endothelin receptor antagonists useful in treatment of diseases)
RN 887366-70-3 HCAPLUS

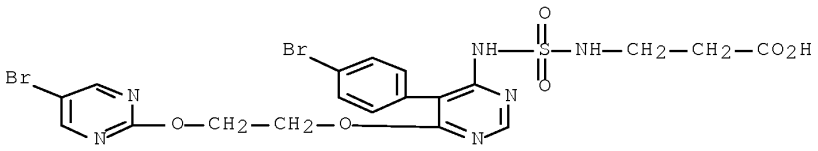
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(3-hydroxypropyl)- (CA INDEX NAME)



IT 887366-71-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel pyrimidine-sulfamides as endothelin receptor antagonists useful in treatment of diseases)

RN 887366-71-4 HCAPLUS

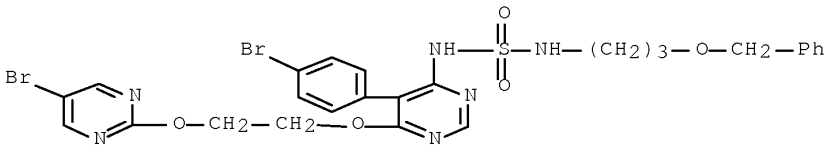
CN β-Alanine, N-[[[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]amino]sulfonyl]- (CA INDEX NAME)



IT 887366-74-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel pyrimidine-sulfamides as endothelin receptor antagonists useful in treatment of diseases)

RN 887366-74-7 HCAPLUS

CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-[3-(phenylmethoxy)propyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN

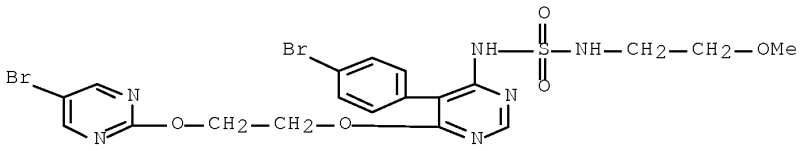
ACCESSION NUMBER: 2004:493689 HCAPLUS Full-text
DOCUMENT NUMBER: 141:54354
TITLE: Preparation of pyrimidine-sulfamides and their use as endothelin receptor antagonist
INVENTOR(S): Bolli, Martin; Boss, Christoph; Clozel, Martine; Fischli, Walter; Weller, Thomas
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd., Switz.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050640	A1	20040617	WO 2003-EP12502	20031110
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2507334	A1	20040617	CA 2003-2507334	20031110
AU 2003285321	A1	20040623	AU 2003-285321	20031110
AU 2003285321	B2	20100408		
EP 1569914	A1	20050907	EP 2003-778307	20031110
EP 1569914	B1	20090218		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003016724	A	20051018	BR 2003-16724	20031110
CN 1711248	A	20051221	CN 2003-80103469	20031110
CN 100379730	C	20080409		
JP 2006509775	T	20060323	JP 2004-556119	20031110
JP 4769460	B2	20110907		
NZ 540937	A	20080630	NZ 2003-540937	20031110
RU 2329255	C2	20080720	RU 2005-120769	20031110
IL 168836	A	20101230	IL 2003-168836	20031110
KR 1063042	B1	20110907	KR 2005-7008632	20031110
NO 2005002520	A	20050627	NO 2005-2520	20050525
MX 2005005793	A	20050816	MX 2005-5793	20050531
US 20070167472	A1	20070719	US 2005-537400	20050602
US 7452896	B2	20081118		
ZA 2005005109	A	20070425	ZA 2005-5109	20050623
IN 2005CN01454	A	20080425	IN 2005-CN1454	20050629

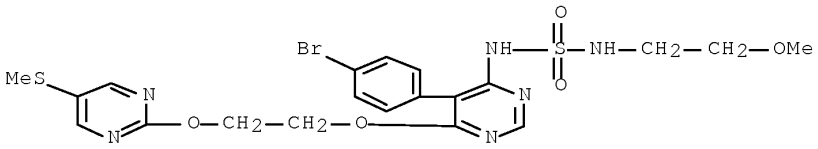
PRIORITY APPLN. INFO.:	WO 2002-EP13601	A	20021202
	EP 2003-778307	A	20031110
	WO 2003-EP12502	W	20031110

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 141:54354; MARPAT 141:54354
IT 706811-19-0P 706811-20-3P 706811-21-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrimidine-sulfamides and their use as endothelin receptor antagonist)

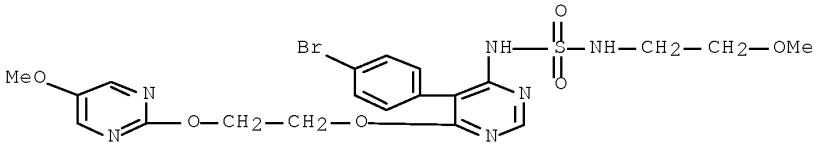
RN 706811-19-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-methoxyethyl)- (CA INDEX NAME)



RN 706811-20-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-methoxyethyl)- (CA INDEX NAME)



RN 706811-21-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-methoxyethyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2002:521730 HCAPLUS Full-text
DOCUMENT NUMBER: 137:93766
TITLE: Preparation of novel pyrimidine-sulfamides as endothelin receptor antagonists
INVENTOR(S): Bolli, Martin; Boss, Christoph; Fischli, Walter; Clozel, Martine; Weller, Thomas
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd., Switz.
SOURCE: PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002053557	A1	20020711	WO 2001-EP14182		20011204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2431675	A1	20020711	CA 2001-2431675		20011204
CA 2431675	C	20111108			
AU 2002227984	A1	20020716	AU 2002-227984		20011204
AU 2002227984	B2	20061207			
EP 1345920	A1	20030924	EP 2001-989570		20011204
EP 1345920	B1	20060412			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2001016237	A	20030930	BR 2001-16237		20011204
JP 2004517855	T	20040617	JP 2002-554676		20011204
JP 4245130	B2	20090325			
CN 1524079	A	20040825	CN 2001-820481		20011204
CN 100432070	C	20081112			
NZ 525614	A	20050324	NZ 2001-525614		20011204
AT 323079	T	20060415	AT 2001-989570		20011204
EP 1693372	A1	20060823	EP 2006-7371		20011204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
PT 1345920	E	20060831	PT 2001-989570		20011204
ES 2260318	T3	20061101	ES 2001-989570		20011204
HU 2003001654	A2	20070328	HU 2003-1654		20011204
HU 2003001654	A3	20070828			
IL 155805	A	20090211	IL 2001-155805		20011204
TW 303245	B	20081121	TW 2001-130769		20011212
ZA 2003003695	A	20040813	ZA 2003-3695		20030513
US 20040077670	A1	20040422	US 2003-433041		20030527
US 7094781	B2	20060822			
MX 2003004780	A	20040521	MX 2003-4780		20030529
NO 2003002699	A	20030613	NO 2003-2699		20030613
NO 324952	B1	20080114			
KR 819668	B1	20080404	KR 2003-7008013		20030616
US 20060178365	A1	20060810	US 2006-400697		20060407
US 7285549	B2	20071023			
PRIORITY APPLN. INFO.:			WO 2000-EP12890	W	20001218
			EP 2001-989570	A3	20011204
			WO 2001-EP14182	W	20011204
			US 2003-433041	A1	20030527

OTHER SOURCE(S): MARPAT 137:93766

IT 441795-23-9P 441795-24-0P 441795-25-1P
441795-27-3P 441795-28-4P 441795-29-5P
441795-30-8P 441795-31-9P 441795-32-0P
441795-33-1P 441795-35-3P 441795-36-4P
441795-38-6P 441795-39-7P 441795-41-1P
441795-42-2P 441796-09-4P 441796-10-7P

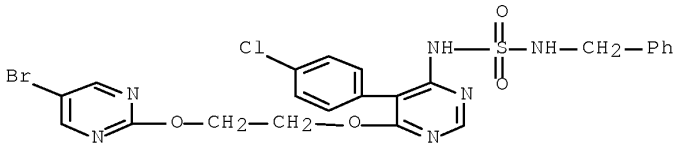
441796-11-8P 441796-13-0P 441796-14-1P
441796-16-3P 441796-17-4P 441796-18-5P
441796-19-6P 441796-20-9P 441796-21-0P
441796-22-1P 441796-24-3P 441796-25-4P
441796-26-5P 441796-27-6P 441796-28-7P
441796-29-8P 441796-30-1P 441796-53-8P
441796-54-9P 441796-55-0P 441797-94-0P
441797-95-1P 441797-96-2P 441797-97-3P
441797-98-4P 441797-99-5P 441798-00-1P
441798-01-2P 441798-02-3P 441798-03-4P
441798-04-5P 441798-05-6P 441798-06-7P
441798-07-8P 441798-08-9P 441798-09-0P
441798-10-3P 441798-11-4P 441798-12-5P
441798-13-6P 441798-14-7P 441798-15-8P
441798-17-0P 441798-18-1P 441798-19-2P
441798-20-5P 441798-21-6P 441798-22-7P
441798-23-8P 441798-24-9P 441798-25-0P
441798-26-1P 441798-27-2P 441798-28-3P
441798-29-4P 441798-30-7P 441798-31-8P
441798-32-9P 441798-33-0P 441798-34-1P
441798-35-2P 441798-36-3P 441798-37-4P
441798-38-5P 441798-39-6P 441798-40-9P
441798-41-0P 441798-42-1P 441798-51-2P
441798-52-3P 441798-53-4P 441798-54-5P
441798-55-6P 441798-56-7P 441798-57-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrimidine-sulfamides as endothelin receptor antagonists)

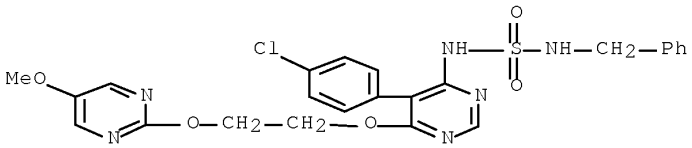
RN 441795-23-9 HCAPLUS

CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



RN 441795-24-0 HCAPLUS

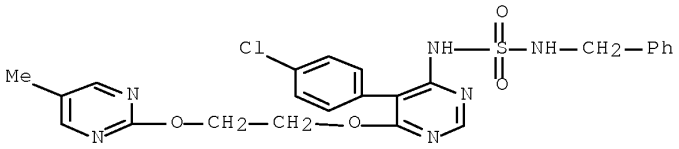
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



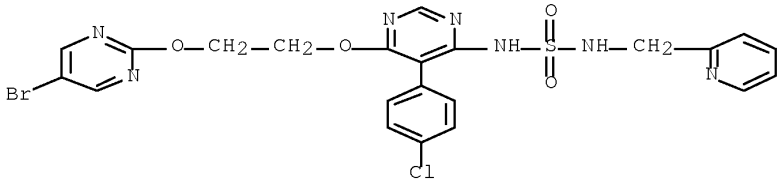
RN 441795-25-1 HCAPLUS

CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methyl-2-pyrimidinyl)oxy]ethoxy]-

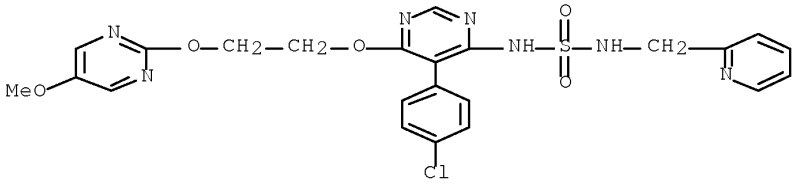
4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



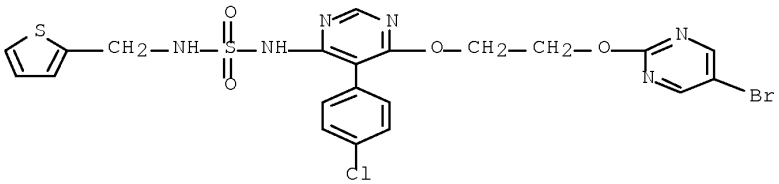
RN 441795-27-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



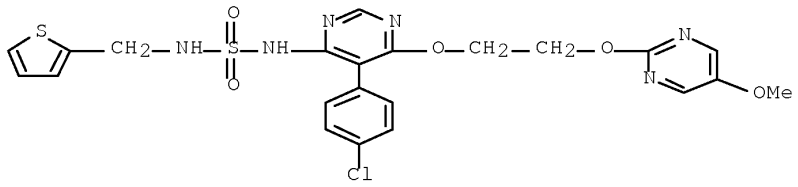
RN 441795-28-4 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



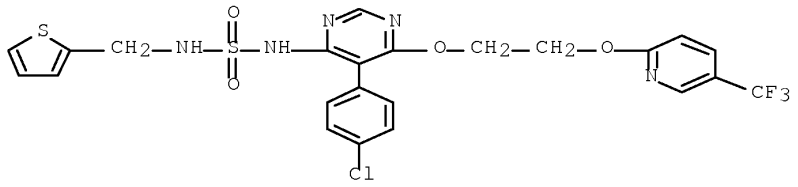
RN 441795-29-5 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



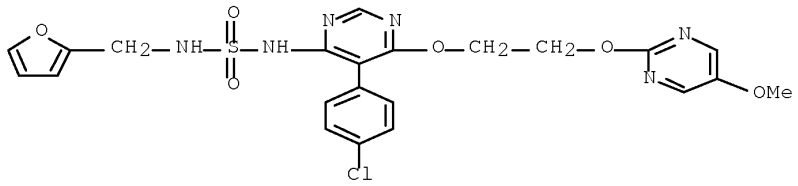
RN 441795-30-8 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



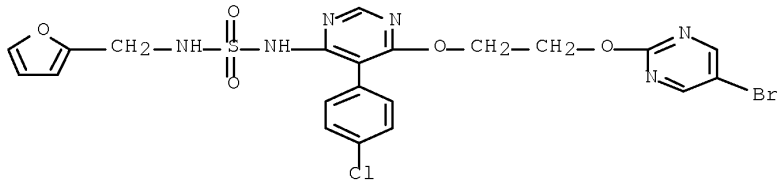
RN 441795-31-9 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



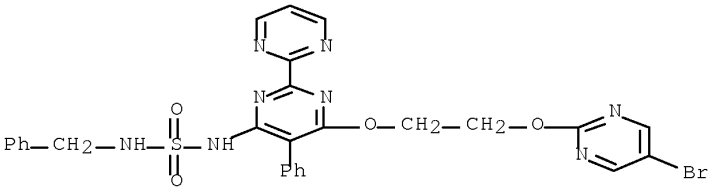
RN 441795-32-0 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)



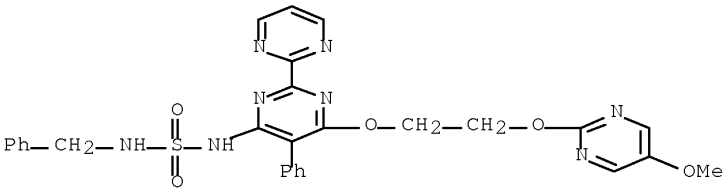
RN 441795-33-1 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)



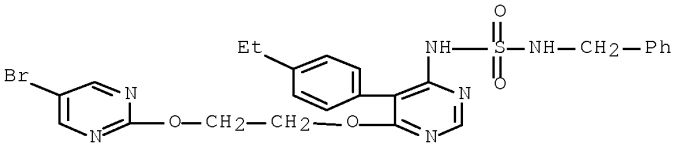
RN 441795-35-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-phenyl[2,2'-bipyrimidin]-4-yl]-N'-(phenylmethyl)- (CA INDEX NAME)



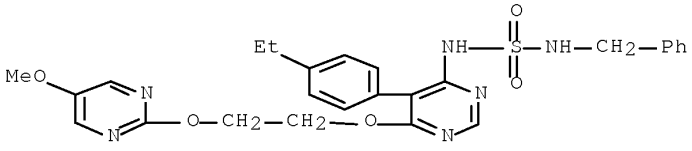
RN 441795-36-4 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-5-phenyl[2,2'-bipyrimidin]-4-yl]-N'-(phenylmethyl)- (CA INDEX NAME)



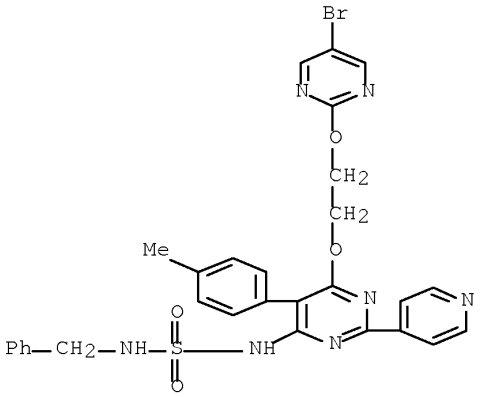
RN 441795-38-6 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-ethylphenyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



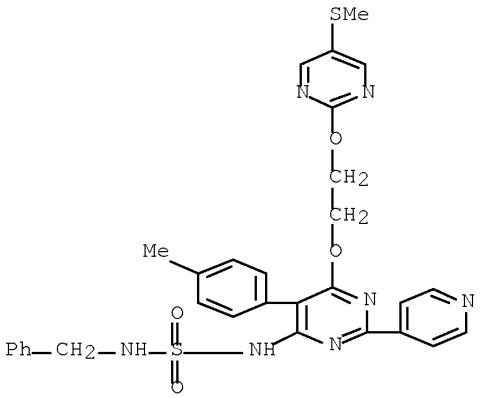
RN 441795-39-7 HCAPLUS
CN Sulfamide, N-[5-(4-ethylphenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



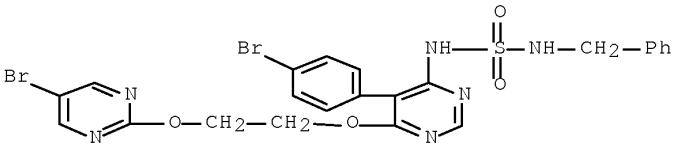
RN 441795-41-1 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-2-(4-pyridinyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



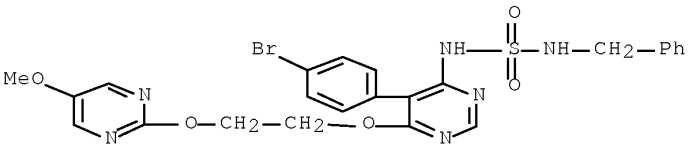
RN 441795-42-2 HCAPLUS
CN Sulfamide, N-[5-(4-methylphenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-2-(4-pyridinyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



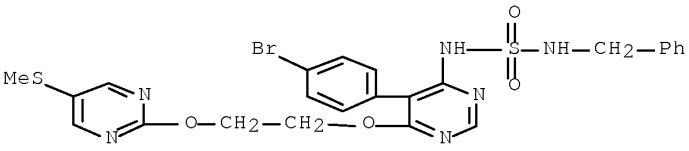
RN 441796-09-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



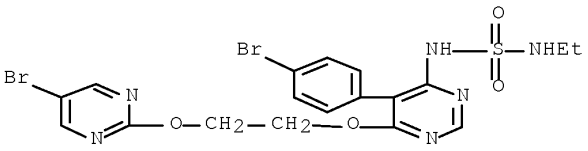
RN 441796-10-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



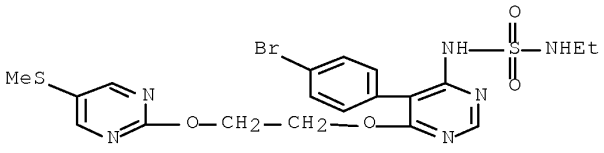
RN 441796-11-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



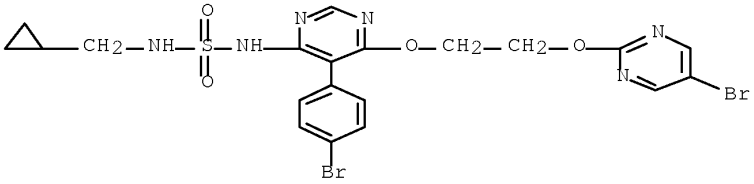
RN 441796-13-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



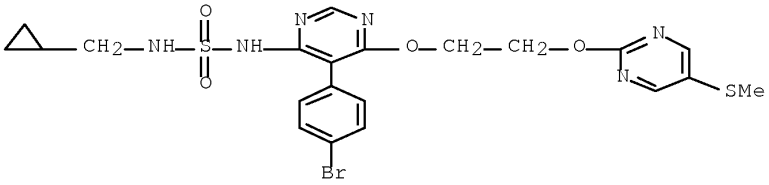
RN 441796-14-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



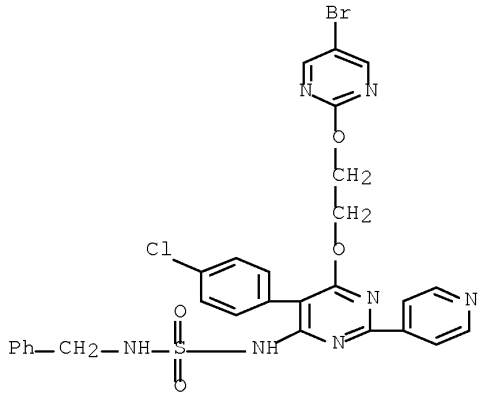
RN 441796-16-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



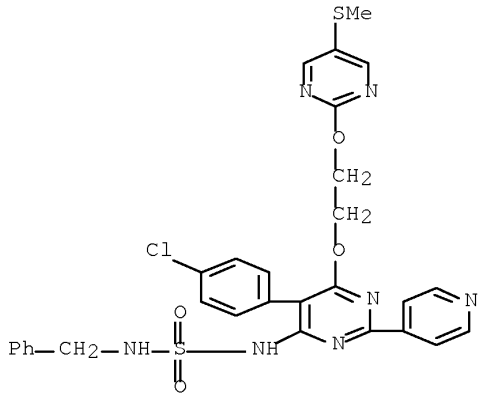
RN 441796-17-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



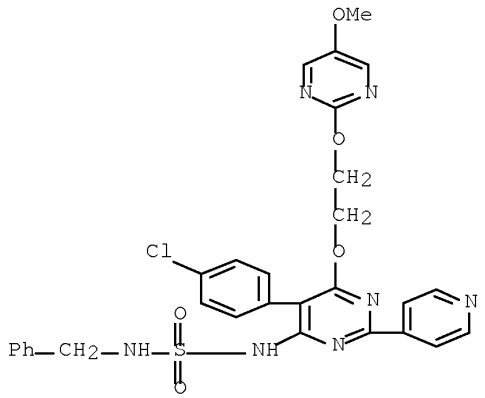
RN 441796-18-5 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-2-(4-pyridinyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



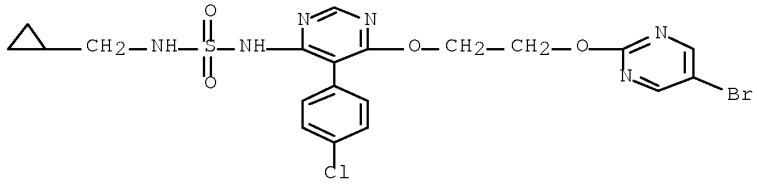
RN 441796-19-6 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-2-(4-pyridinyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



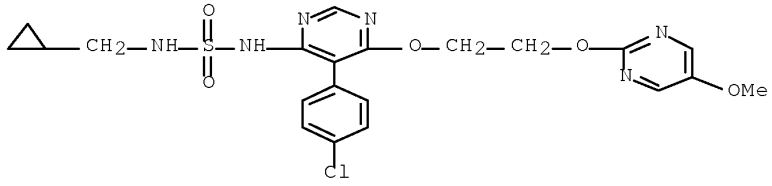
RN 441796-20-9 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-2-(4-pyridinyl)-4-pyrimidinyl]-N'-(phenylmethyl)- (CA INDEX NAME)



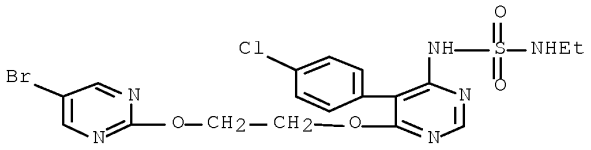
RN 441796-21-0 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



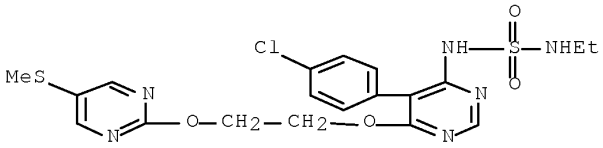
RN 441796-22-1 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



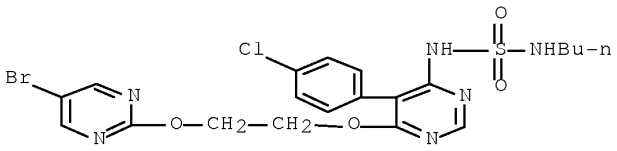
RN 441796-24-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



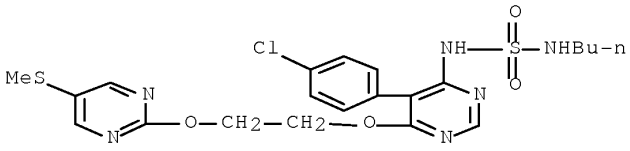
RN 441796-25-4 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



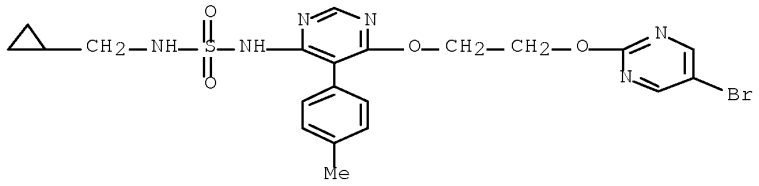
RN 441796-26-5 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-butyl- (CA INDEX NAME)



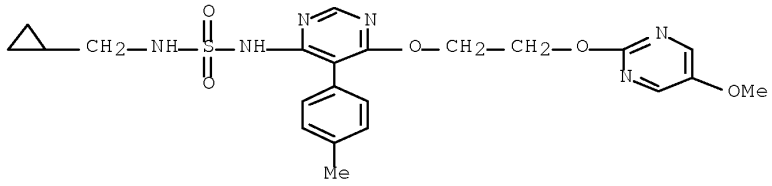
RN 441796-27-6 HCAPLUS
CN Sulfamide, N-butyl-N'-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]- (CA INDEX NAME)



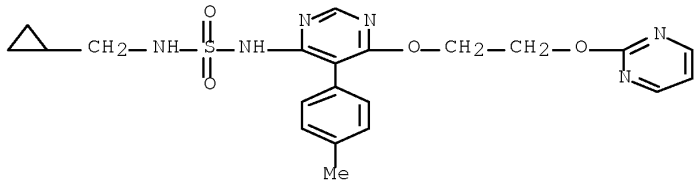
RN 441796-28-7 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



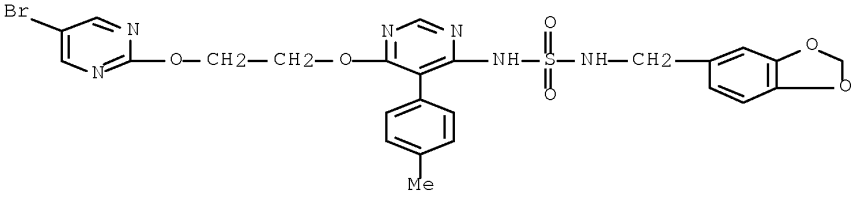
RN 441796-29-8 HCAPLUS
CN Sulfamide, N-(cyclopropylmethyl)-N'-[6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-4-pyrimidinyl]- (CA INDEX NAME)



RN 441796-30-1 HCAPLUS
CN Sulfamide, N-(cyclopropylmethyl)-N'-[5-(4-methylphenyl)-6-[2-(2-pyrimidinyloxy)ethoxy]-4-pyrimidinyl]- (CA INDEX NAME)

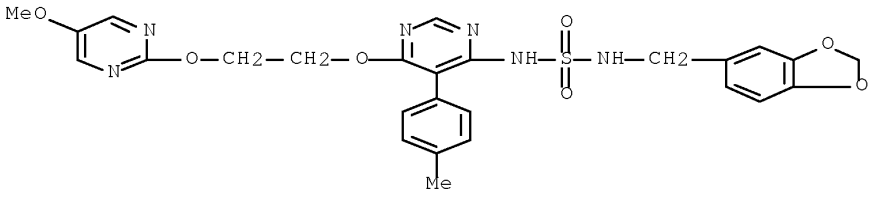


RN 441796-53-8 HCAPLUS
CN Sulfamide, N-(1,3-benzodioxol-5-ylmethyl)-N'-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-4-pyrimidinyl]- (CA INDEX NAME)

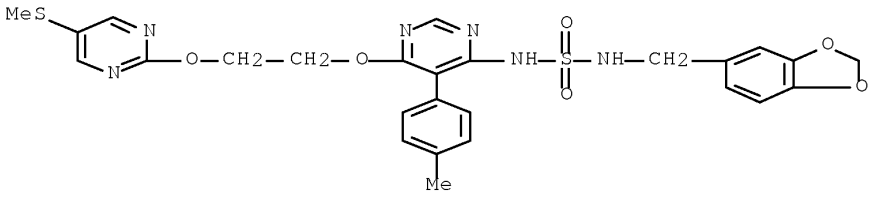


RN 441796-54-9 HCAPLUS

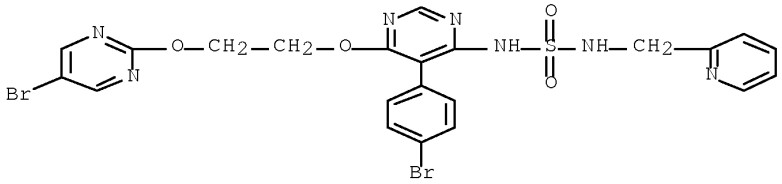
CN Sulfamide, N-(1,3-benzodioxol-5-ylmethyl)-N'-[6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-5-(4-methylphenyl)-4-pyrimidinyl]- (CA INDEX NAME)



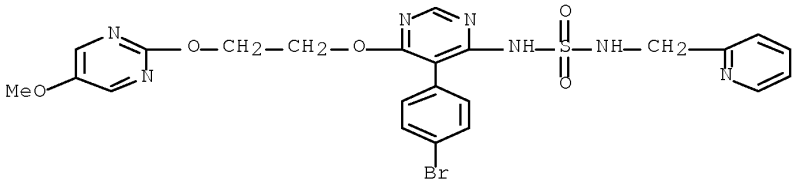
RN 441796-55-0 HCAPLUS
CN Sulfamide, N-(1,3-benzodioxol-5-ylmethyl)-N'-[5-(4-methylphenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]- (CA INDEX NAME)



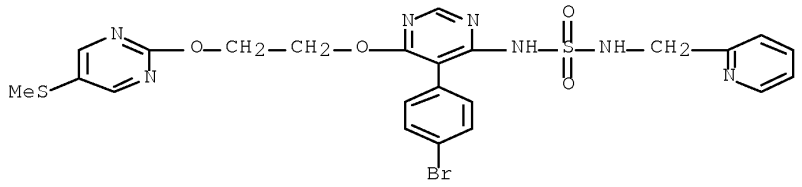
RN 441797-94-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



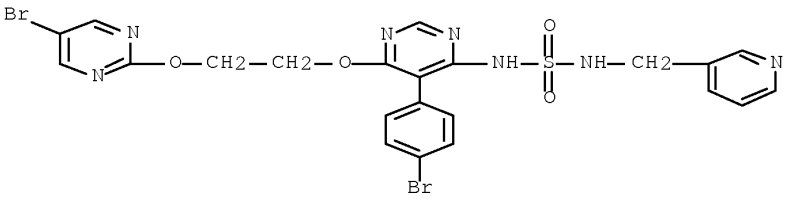
RN 441797-95-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



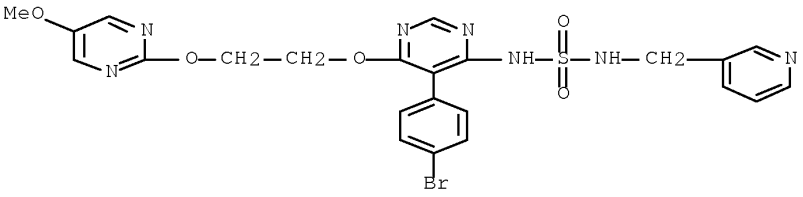
RN 441797-96-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



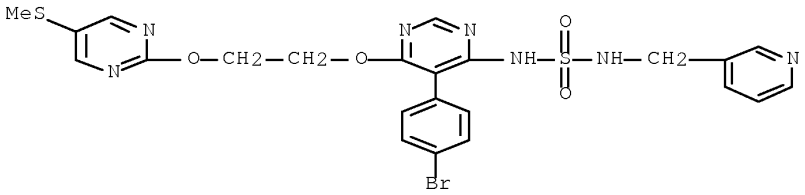
RN 441797-97-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



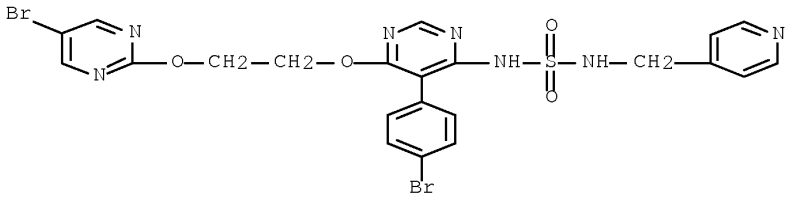
RN 441797-98-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



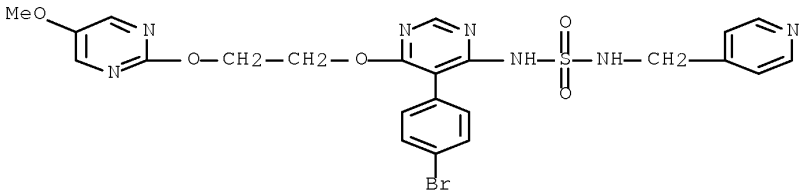
RN 441797-99-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



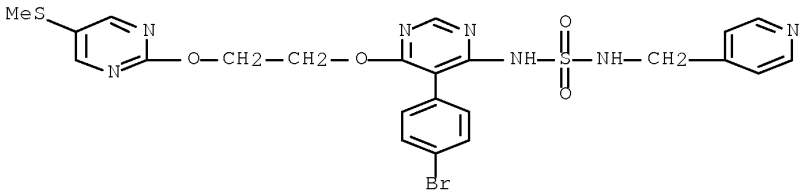
RN 441798-00-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)



RN 441798-01-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)

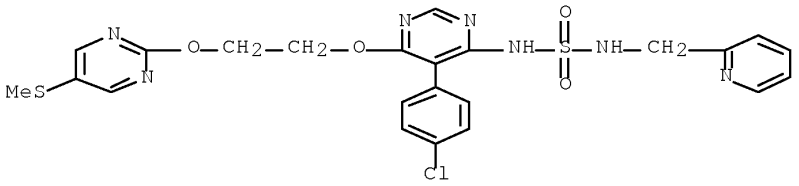


RN 441798-02-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)

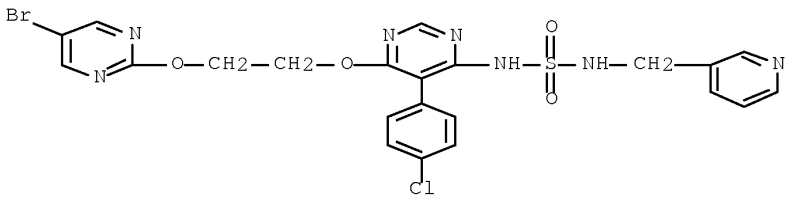


RN 441798-03-4 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-

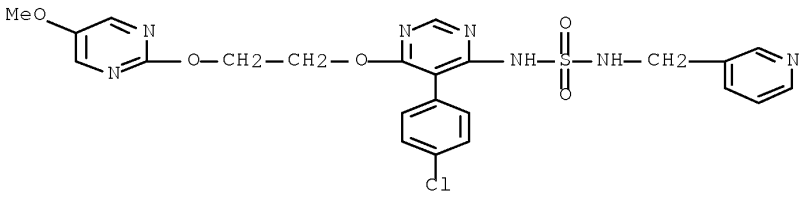
pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-pyridinylmethyl)- (CA INDEX NAME)



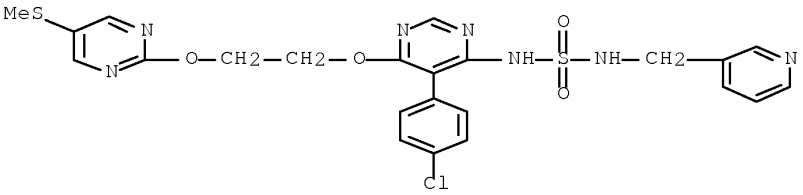
RN 441798-04-5 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



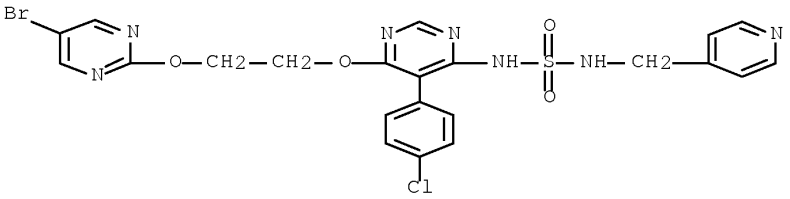
RN 441798-05-6 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



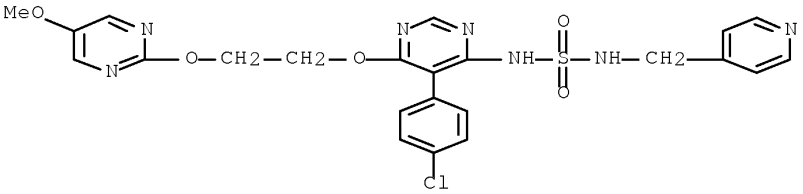
RN 441798-06-7 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(3-pyridinylmethyl)- (CA INDEX NAME)



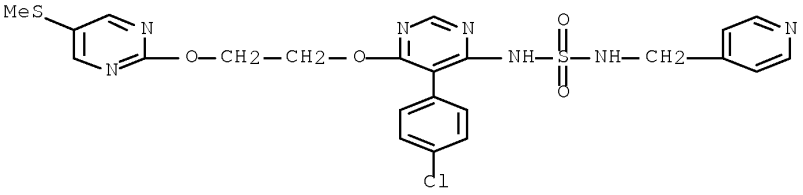
RN 441798-07-8 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)



RN 441798-08-9 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)

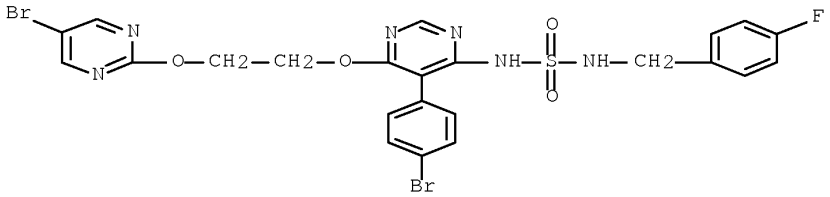


RN 441798-09-0 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(4-pyridinylmethyl)- (CA INDEX NAME)

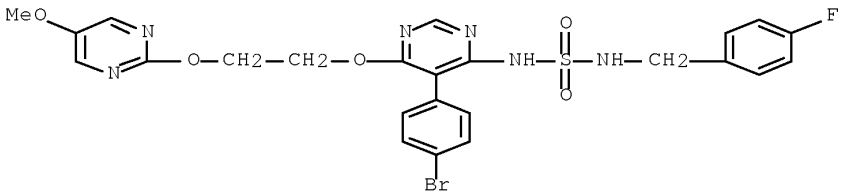


RN 441798-10-3 HCAPLUS

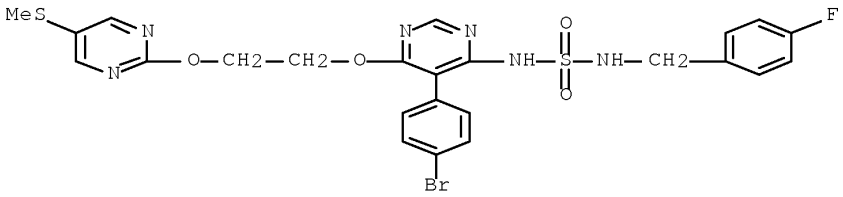
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



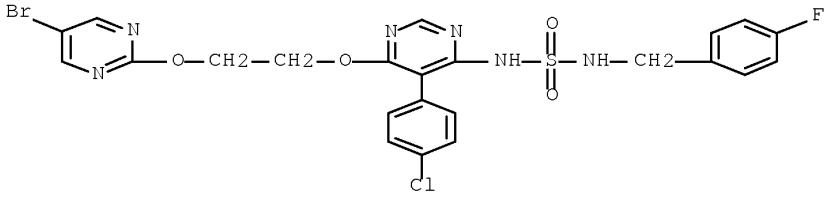
RN 441798-11-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



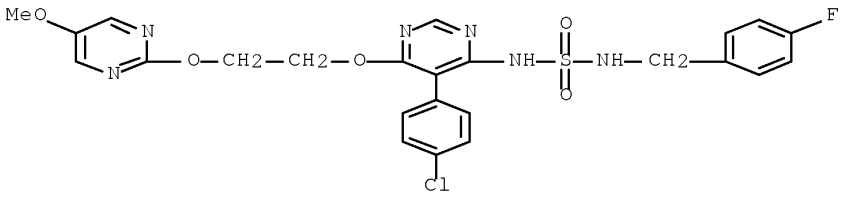
RN 441798-12-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



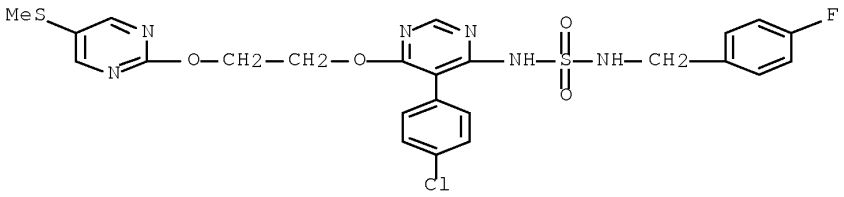
RN 441798-13-6 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



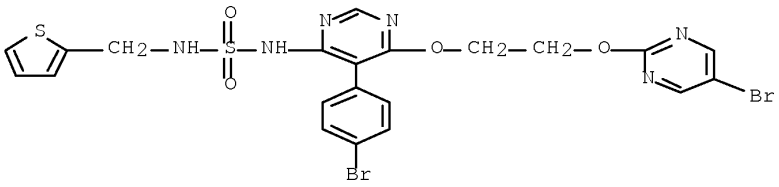
RN 441798-14-7 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



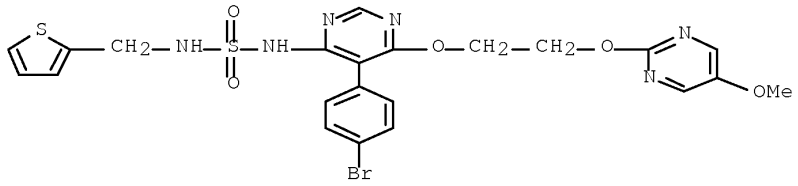
RN 441798-15-8 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-[(4-fluorophenyl)methyl]- (CA INDEX NAME)



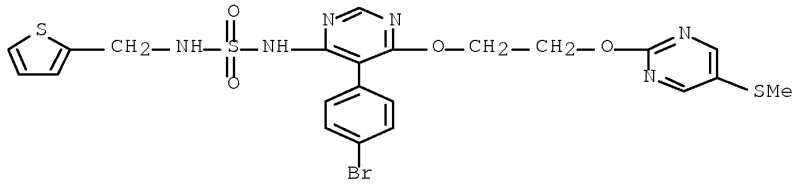
RN 441798-17-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



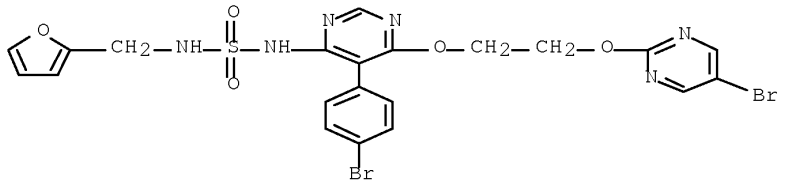
RN 441798-18-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



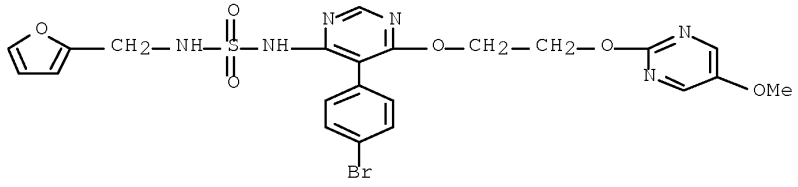
RN 441798-19-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



RN 441798-20-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)

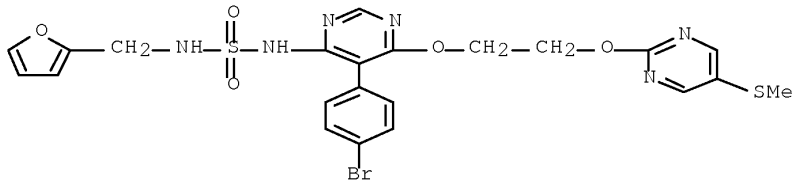


RN 441798-21-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)

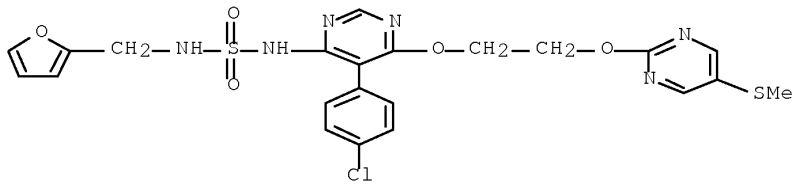


RN 441798-22-7 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-

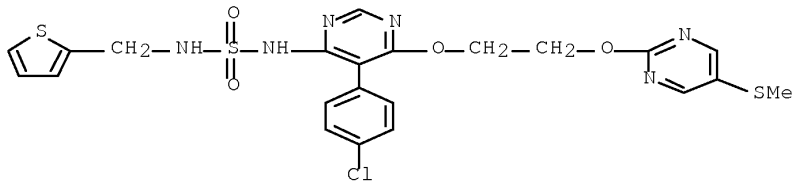
pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)



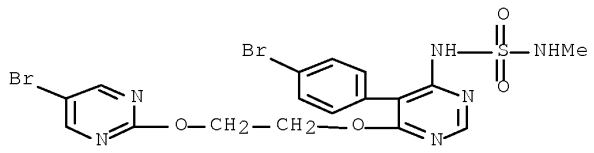
RN 441798-23-8 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-furanylmethyl)- (CA INDEX NAME)



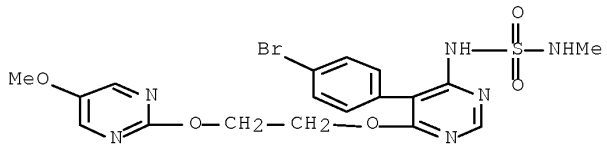
RN 441798-24-9 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-thienylmethyl)- (CA INDEX NAME)



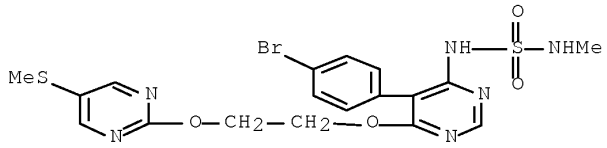
RN 441798-25-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



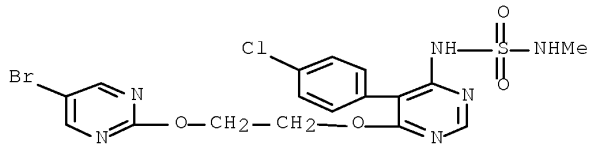
RN 441798-26-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



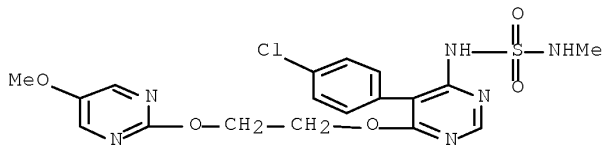
RN 441798-27-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



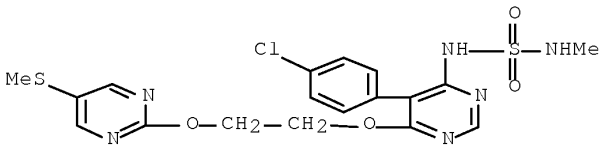
RN 441798-28-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



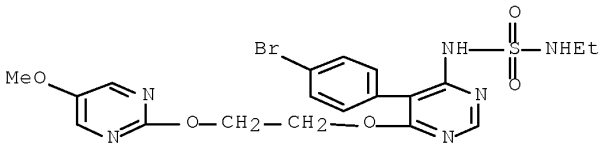
RN 441798-29-4 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



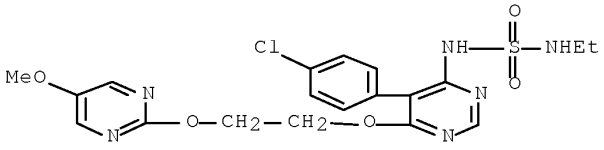
RN 441798-30-7 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-methyl- (CA INDEX NAME)



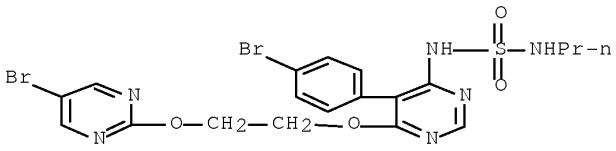
RN 441798-31-8 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)



RN 441798-32-9 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-ethyl- (CA INDEX NAME)

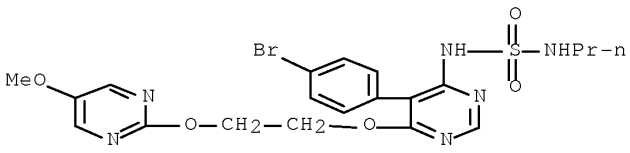


RN 441798-33-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)

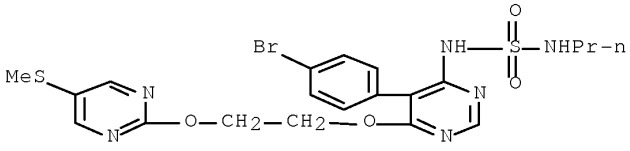


RN 441798-34-1 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-

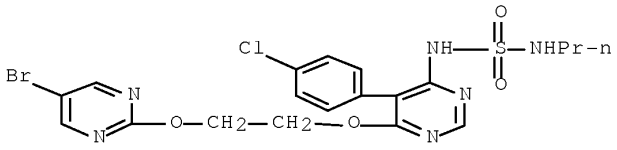
4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



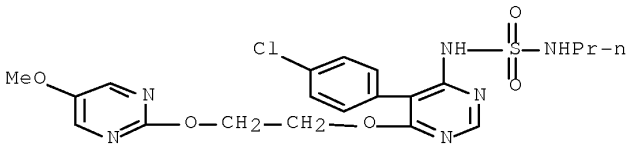
RN 441798-35-2 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



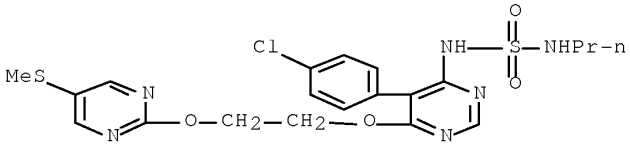
RN 441798-36-3 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



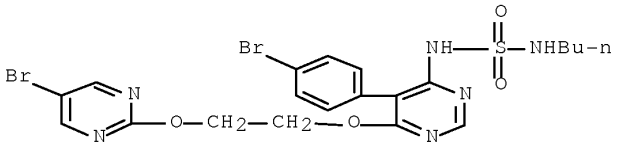
RN 441798-37-4 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



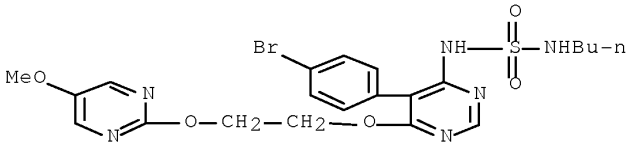
RN 441798-38-5 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-propyl- (CA INDEX NAME)



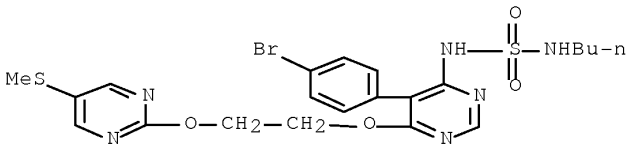
RN 441798-39-6 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-butyl- (CA INDEX NAME)



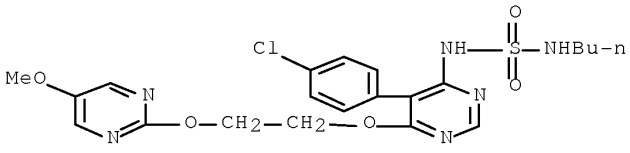
RN 441798-40-9 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-butyl- (CA INDEX NAME)



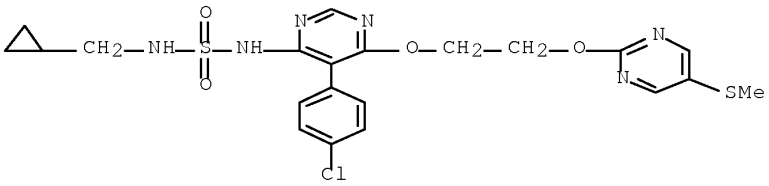
RN 441798-41-0 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-butyl- (CA INDEX NAME)



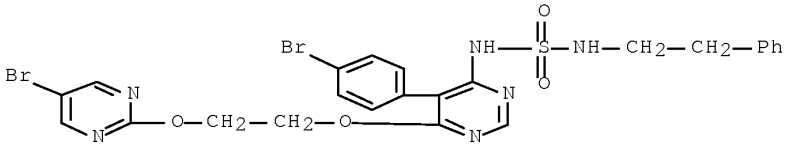
RN 441798-42-1 HCAPLUS
CN Sulfamide, N-butyl-N'-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]- (CA INDEX NAME)



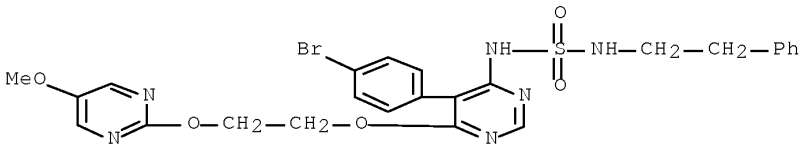
RN 441798-51-2 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(cyclopropylmethyl)- (CA INDEX NAME)



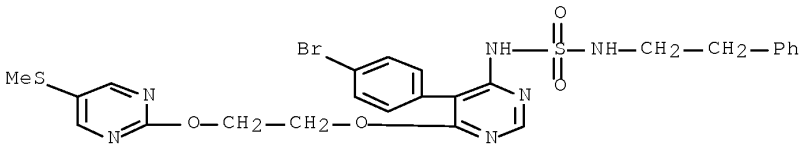
RN 441798-52-3 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



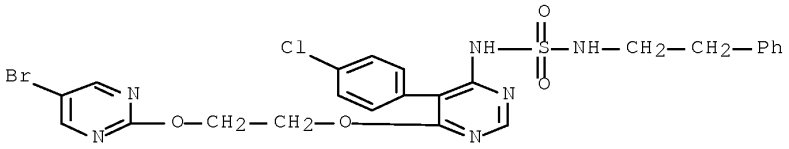
RN 441798-53-4 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



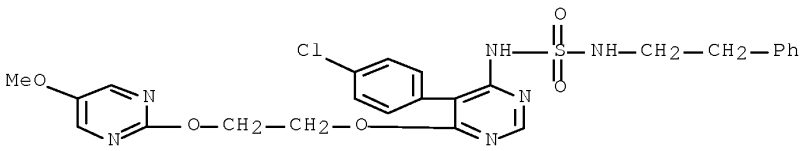
RN 441798-54-5 HCAPLUS
CN Sulfamide, N-[5-(4-bromophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



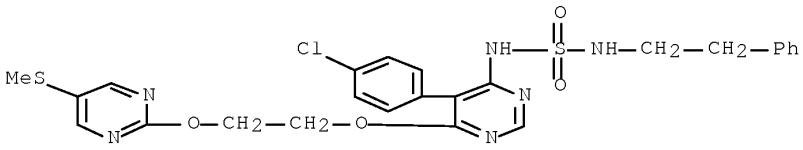
RN 441798-55-6 HCAPLUS
CN Sulfamide, N-[6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-5-(4-chlorophenyl)-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



RN 441798-56-7 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[(5-methoxy-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



RN 441798-57-8 HCAPLUS
CN Sulfamide, N-[5-(4-chlorophenyl)-6-[2-[[5-(methylthio)-2-pyrimidinyl]oxy]ethoxy]-4-pyrimidinyl]-N'-(2-phenylethyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	127.72	332.25

STN INTERNATIONAL LOGOFF AT 12:35:33 ON 12 DEC 2012

Connecting via Winsock to STN at pto-stn on port 23

Welcome to STN International! Enter x:X

LOGINID:SSPTAKDC1617

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1	FEB 1	Instructor-led and on-demand STN training options available from CAS
NEWS	2	SEP 01	Older Versions of STN Express to be Discontinued Beginning in March 2012
NEWS	3	APR 9	CAS Expands Global Patent Coverage - The Eurasian Patent Organization Becomes 63rd Authority on CA/CAplus
NEWS	4	APR 16	DWPI Database (WPINDEX, WPIDS, WPIX) Enhanced with Numerical Property Search Feature
NEWS	5	APR 23	RSS Delivery for STN Alerts (SDIs) is Now Available on STN
NEWS	6	MAY 9	INIS, BABS and GMELIN97 Databases Removed from STN
NEWS	7	MAY 21	Reload of FSTA Database
NEWS	8	MAY 21	Search DOIs in CA/CAplus on STN
NEWS	9	MAY 23	Get the Latest Version of STN Express, Version 8.5.1!
NEWS	10	MAY 30	INPADOC Databases-Update on Japanese Legal Status Information
NEWS	11	MAY 30	INPADOC Databases-Enhanced Coverage of US Citation Data
NEWS	12	JUN 01	INPADOCDB: Legal Status in Original Language Available
NEWS	13	JUN 11	Keep Current with Weekly SDI Packages Now Available on STN
NEWS	14	JUL 05	More Frequent Updates to the Emtree Thesaurus in Embase on STN Provide Earlier Access to the Latest Drug and Medical Terminology
NEWS	15	JUL 18	INPADOCDB: Enhanced Display Options
NEWS	16	JUL 19	Upcoming Reload of AEROSPACE: Effect on SDIs, Manual Profiles and Saved Answers

```
 NEWS 17  JUL 30  Launch of new PQSciTech Database, Created from 25 Individual
                  CSA Databases Allows More Efficient Searching on STN
 NEWS 18  JUL 30  Reload of ENCOMPPAT/2 Databases
 NEWS 19  JUL 30  More Experimental Property Data in CAS REGISTRY
 NEWS 20  AUG  1  Reload of ReaxysFile on STN - Significantly More Content Added
                  and Updates are Resumed
 NEWS 21  AUG  1  Redesigned CAS Website to be Launched on August 5, 2012
 NEWS 22  AUG  6  INPADOC: German Patent Coverage Resumed
 NEWS 23  SEP 10  Get More Current Reaction Information with Daily Updates to
                  CASREACT
 NEWS 24  SEP 10  Predict when CAS REGISTRY Hits 70 Million
 NEWS 25  SEP 20  Reload of METADEX - Effect on SDIs and Saved Answers
 NEWS 26  SEP 24  Expanded Embase Database Coverage on STN Includes More
                  Biomedical and Pharmacological Content from Conferences
 NEWS 27  OCT 19  MARPAT Backfile Expansion Update
 NEWS 28  OCT 23  Embase's Emtree Thesaurus Updated
 NEWS 29  OCT 29  New Japanese Full-Text Patent Database Now Available on STN
 NEWS 30  NOV 13  Upcoming Reload of AGRICOLA - Effect on SDIs, Manual Profiles
                  and Saved Answers
 NEWS 31  NOV 19  Reload of IMSPATENTS - Effect on SDIs, Manual profiles and
                  Saved answers
 NEWS 32  NOV 27  INPADOC: The New Cooperative Patent Classification Is Now
                  Available.
 NEWS 33  DEC  3  Enhanced CASREACT Coverage on STN - A New Source of Prior Art
 NEWS 34  DEC 10  New SDI STANDARD Option Streamlines SDI Set-ups on STN

 NEWS EXPRESS 23 MAY 2012 CURRENT WINDOWS VERSION IS V8.5.1,
              AND CURRENT DISCOVER FILE IS DATED 11 DECEMBER 2012.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS TRAINING Find instructor-led and self-directed training opportunities

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN customer
  agreement.  This agreement limits use to scientific research.  Use
  for software development or design, implementation of commercial
  gateways, or use of CAS and STN data in the building of commercial
  products is prohibited and may result in loss of user privileges
  and other penalties.

* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:48:14 ON 12 DEC 2012

=>
Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?
Choice (Y/n):
Switching to the Registry File...
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> FILE REGISTRY
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.24	0.24

FILE 'REGISTRY' ENTERED AT 13:48:37 ON 12 DEC 2012
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2012 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 11 DEC 2012 HIGHEST RN 1413972-79-8
DICTIONARY FILE UPDATES: 11 DEC 2012 HIGHEST RN 1413972-79-8

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

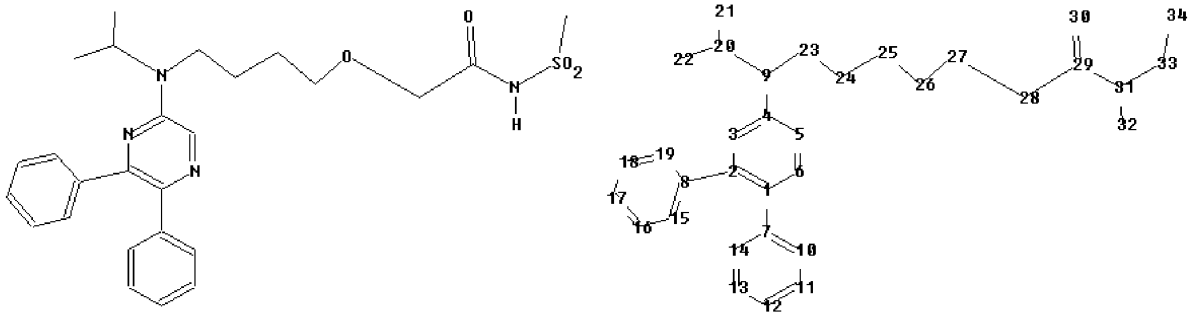
TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 2012

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

=>
Uploading C:\Users\kcarter\Documents\STN Express 8.4\Queries\13604148B.str



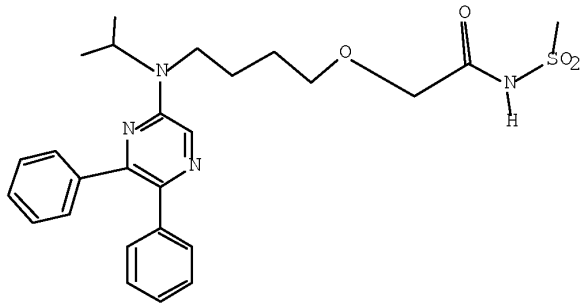
chain nodes :
9 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
ring nodes :
1 2 3 4 5 6 7 8 10 11 12 13 14 15 16 17 18 19
chain bonds :
1-7 2-8 4-9 9-20 9-23 20-21 20-22 23-24 24-25 25-26 26-27 27-28 28-29
29-30 29-31 31-32 31-33 33-34
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-10 7-14 8-15 8-19 10-11 11-12 12-13 13-14
15-16 16-17 17-18 18-19
exact/norm bonds :
4-9 9-20 9-23 26-27 27-28 29-30 29-31 31-33
exact bonds :
1-7 2-8 20-21 20-22 23-24 24-25 25-26 28-29 31-32 33-34

normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-10 7-14 8-15 8-19 10-11 11-12 12-13 13-14
15-16 16-17 17-18 18-19

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:CLASS 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 full
FULL SEARCH INITIATED 13:49:00 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 100 TO ITERATE

100.0% PROCESSED 100 ITERATIONS 86 ANSWERS
SEARCH TIME: 00.00.01

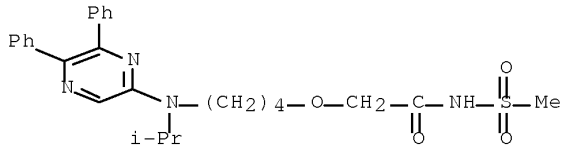
L2 86 SEA SSS FUL L1

=> d 1-10

L2 ANSWER 1 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1267423-56-2 REGISTRY
ED Entered STN: 09 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, compd. with 2-(dimethylamino)ethanol (1:1) (CA INDEX NAME)
MF C26 H32 N4 O4 S . C4 H11 N O
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

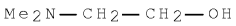
CM 1

CRN 475086-01-2
CMF C26 H32 N4 O4 S



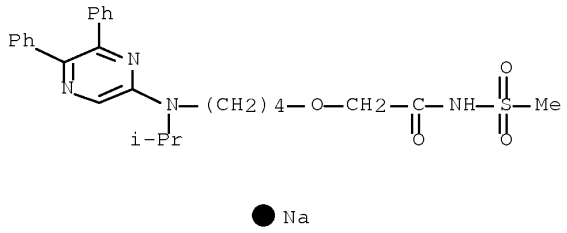
CM 2

CRN 108-01-0
CMF C4 H11 N O



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

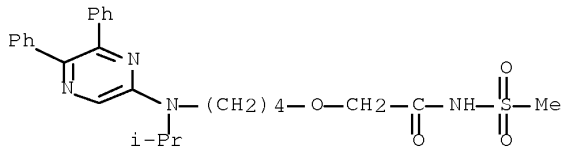
L2 ANSWER 2 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1267423-51-7 REGISTRY
ED Entered STN: 09 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, sodium salt (1:1) (CA INDEX NAME)
MF C26 H32 N4 O4 S . Na
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
CRN (475086-01-2)



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 3 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1267423-49-3 REGISTRY
ED Entered STN: 09 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, potassium salt (1:1) (CA INDEX NAME)
MF C26 H32 N4 O4 S . K

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
CRN (475086-01-2)



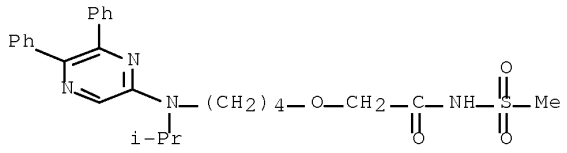


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 4 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1267423-47-1 REGISTRY
ED Entered STN: 09 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, compd. with 2-methyl-2-propanamine (1:1) (CA INDEX NAME)
MF C26 H32 N4 O4 S . C4 H11 N
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

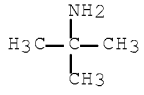
CM 1

CRN 475086-01-2
CMF C26 H32 N4 O4 S



CM 2

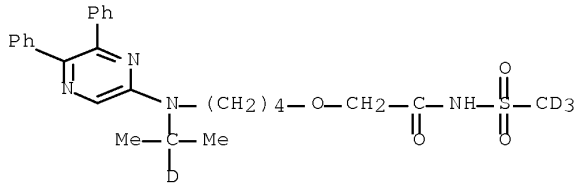
CRN 75-64-9
CMF C4 H11 N



1 REFERENCES IN FILE CA (1907 TO DATE)

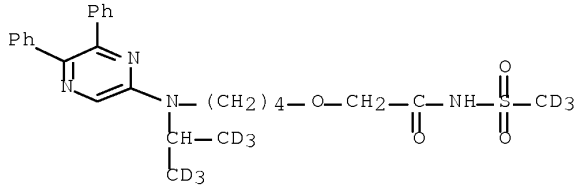
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 5 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-34-1 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H28 D4 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



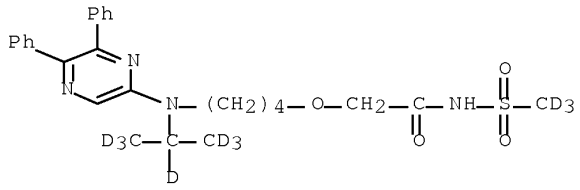
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 6 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-33-0 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H23 D9 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



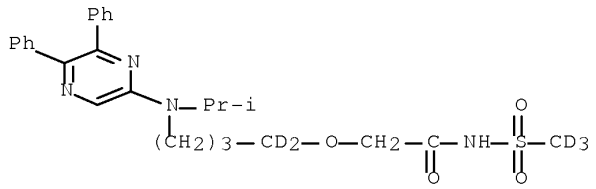
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 7 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-32-9 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H22 D10 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



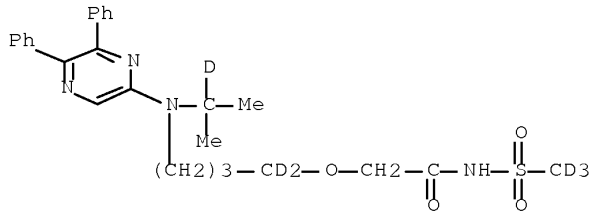
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 8 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-31-8 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H27 D5 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

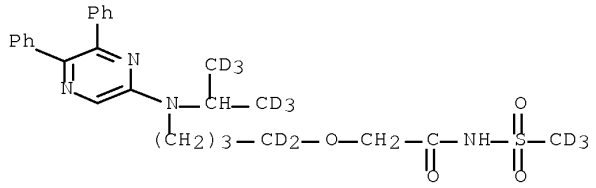
L2 ANSWER 9 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-30-7 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H26 D6 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 10 OF 86 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265296-29-4 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)
MF C26 H21 D11 N4 O4 S
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> display set notice

SET PARAMETER	CURRENT	PERMANENT	LOGIN	DEFAULT
NOTICE (USD)				
DISPLAY	'OFF'		'OFF'	'100'
SEARCH	'1000'		'1000'	'1000'

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	226.81	227.05

FILE 'REGISTRY' ENTERED AT 13:50:20 ON 12 DEC 2012
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2012 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 DEC 2012 HIGHEST RN 1413972-79-8
DICTIONARY FILE UPDATES: 11 DEC 2012 HIGHEST RN 1413972-79-8

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 2012

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

=> S 1267423-56-2/RN

L3 1 1267423-56-2/RN

=> SET NOTICE 1 DISPLAY

NOTICE SET TO 1 U.S. DOLLAR FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=> D L3 RN CCN 1-

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y
THE ESTIMATED COST FOR THIS REQUEST IS 2.20 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y

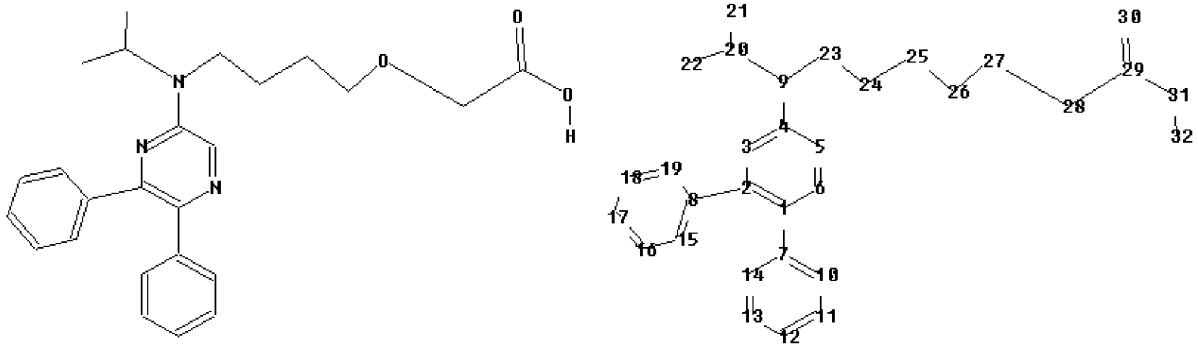
L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1267423-56-2 REGISTRY
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, compd. with 2-(dimethylamino)ethanol (1:1) (CA INDEX NAME)

=> SET NOTICE OFF DISPLAY

NOTICE SET TO OFF FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=>

=>
Uploading C:\Users\kcarter\Documents\STN Express 8.4\Queries\13604148C.str



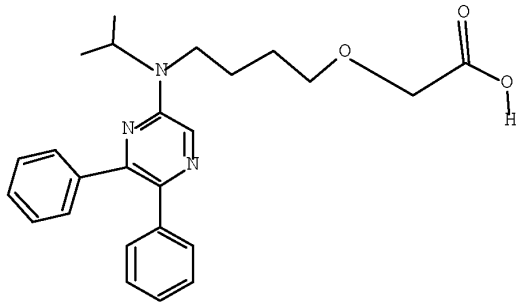
chain nodes :
9 20 21 22 23 24 25 26 27 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 7 8 10 11 12 13 14 15 16 17 18 19

chain bonds :
1-7 2-8 4-9 9-20 9-23 20-21 20-22 23-24 24-25 25-26 26-27 27-28 28-29
29-30 29-31 31-32
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-10 7-14 8-15 8-19 10-11 11-12 12-13 13-14
15-16 16-17 17-18 18-19
exact/norm bonds :
4-9 9-20 9-23 26-27 27-28
exact bonds :
1-7 2-8 20-21 20-22 23-24 24-25 25-26 28-29 31-32
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-10 7-14 8-15 8-19 10-11 11-12 12-13 13-14
15-16 16-17 17-18 18-19 29-30 29-31

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:CLASS 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

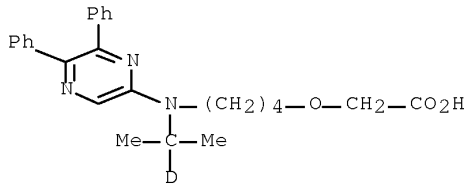
=> s l4 full
FULL SEARCH INITIATED 13:51:06 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 229 TO ITERATE

100.0% PROCESSED 229 ITERATIONS 42 ANSWERS
SEARCH TIME: 00.00.01

L5 42 SEA SSS FUL L4

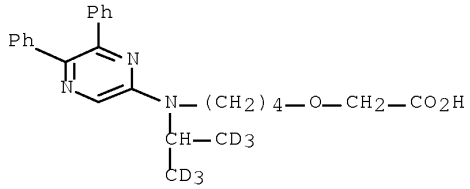
=> d 1-10

L5 ANSWER 1 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-57-5 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy]- (CA INDEX NAME)
MF C25 H28 D N3 O3
SR CA
LC STN Files: CA, CAPLUS



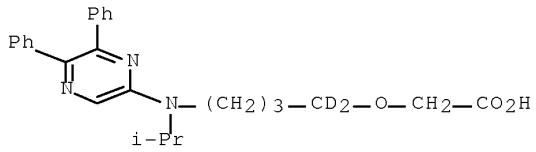
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 2 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-56-4 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy]- (CA INDEX NAME)
MF C25 H23 D6 N3 O3
SR CA
LC STN Files: CA, CAPLUS



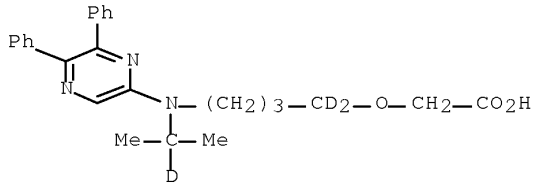
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 3 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-55-3 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1-d2]- (CA INDEX NAME)
MF C25 H27 D2 N3 O3
SR CA
LC STN Files: CA, CAPLUS



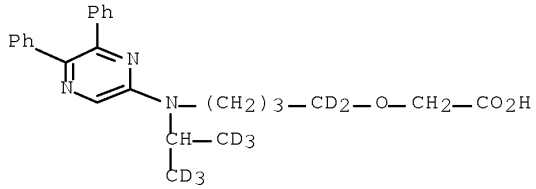
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 4 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-54-2 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1-d2]- (CA INDEX NAME)
MF C25 H26 D3 N3 O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

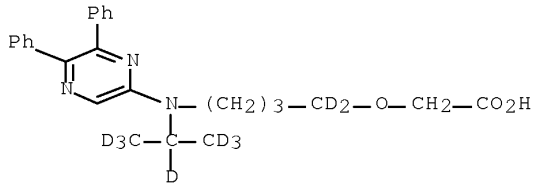
L5 ANSWER 5 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-53-1 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1-d2]- (CA INDEX NAME)
MF C25 H21 D8 N3 O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

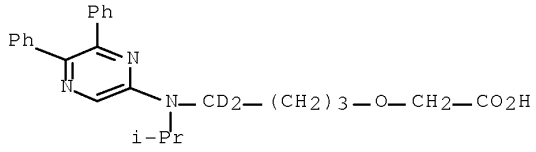
L5 ANSWER 6 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN

RN 1265295-52-0 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1-d2]- (CA INDEX NAME)
MF C25 H20 D9 N3 O3
SR CA
LC STN Files: CA, CAPLUS



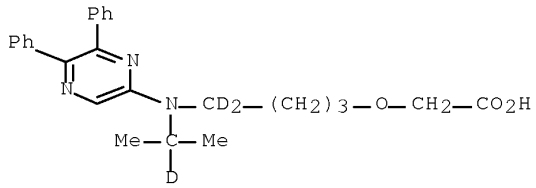
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 7 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-51-9 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-4,4-d2]- (CA INDEX NAME)
MF C25 H27 D2 N3 O3
SR CA
LC STN Files: CA, CAPLUS



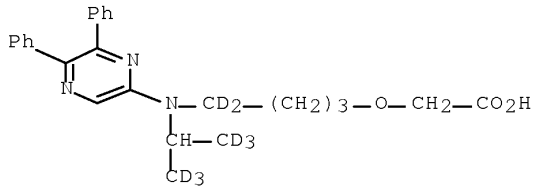
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 8 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-50-8 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-4,4-d2]- (CA INDEX NAME)
MF C25 H26 D3 N3 O3
SR CA
LC STN Files: CA, CAPLUS



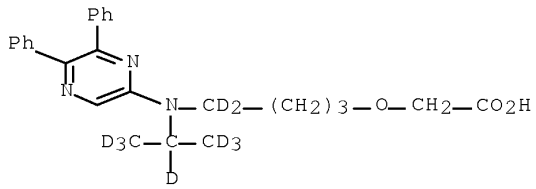
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 9 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-49-5 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-4,4-d2]- (CA INDEX NAME)
MF C25 H21 D8 N3 O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 10 OF 42 REGISTRY COPYRIGHT 2012 ACS on STN
RN 1265295-48-4 REGISTRY
ED Entered STN: 01 Mar 2011
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-4,4-d2]- (CA INDEX NAME)
MF C25 H20 D9 N3 O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=>  display set notice


SET PARAMETER CURRENT  PERMANENT LOGIN  DEFAULT
------------- -------  --------- ------ -------
NOTICE (USD)
  DISPLAY     'OFF'              'OFF'  '100'
  SEARCH      '1000'             '1000' '1000'


=> FIL REGISTRY

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     229.01     456.06

FILE 'REGISTRY' ENTERED AT 13:51:50 ON 12 DEC 2012
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2012 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   11 DEC 2012  HIGHEST RN 1413972-79-8
DICTIONARY FILE UPDATES:  11 DEC 2012  HIGHEST RN 1413972-79-8

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

TSCA INFORMATION NOW CURRENT THROUGH JUNE 29, 2012

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

=> S 1265295-51-9/RN

L6           1 1265295-51-9/RN

=> SET NOTICE 1 DISPLAY

NOTICE SET TO 1 U.S. DOLLAR FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=> D L6 RN CCN 1-

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y
THE ESTIMATED COST FOR THIS REQUEST IS 2.20 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:y
```

```
L6   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2012 ACS on STN
RN   1265295-51-9  REGISTRY
CN   Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-
     4,4-d2]-  (CA INDEX NAME)


=> SET NOTICE OFF DISPLAY

NOTICE SET TO OFF  FOR DISPLAY COMMAND
SET COMMAND COMPLETED

=>

=> file hcaplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   2.72     458.78

FILE 'HCAPLUS' ENTERED AT 13:52:05 ON 12 DEC 2012
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2012 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 12 Dec 2012  VOL 157 ISS 25
FILE LAST UPDATED: 11 Dec 2012  (20121211/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  November 2012
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  November 2012

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the fourth quarter of 2012.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l2
L7          22 L2

=> s l7 and PDE5
          1832 PDE5
L8           0 L7 AND PDE5

=> s l5
L9          20 L5

=> s l5 and PDE5
```

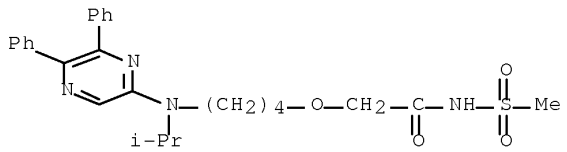
```
           20 L5
         1832 PDE5
L10         0 L5 AND PDE5

=> d l7 ibib hitstr 1-
YOU HAVE REQUESTED DATA FROM 22 ANSWERS - CONTINUE? Y/(N):y

L7   ANSWER 1 OF 22  HCAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:1562497  HCAPLUS Full-text
DOCUMENT NUMBER:         157:624827
TITLE:                   Prostacyclin and analogs thereof administered during
                         surgery for prevention and treatment of capillary
                         leakage
INVENTOR(S):             Johansson, Paer; Ostrowski, Sisse Rye
PATENT ASSIGNEE(S):      Rigshospitalet, Den.
SOURCE:                  PCT Int. Appl., 70pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2012143012         A1    20121026    WO 2012-DK50100         20120330
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
             CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
             ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
             MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
             PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM,
             ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
             ZA, ZM, ZW
         RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
             HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
             SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD,
             SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                       DK 2011-70191       A  20110419
                                             US 2011-476814P     P  20110419

IT   475086-01-2
     RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of
     action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (prostacyclin and analogs thereof administered during surgery for
        prevention and treatment of capillary leakage and effect on biomarker
        levels)
RN   475086-01-2  HCAPLUS
CN   Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-
     (methylsulfonyl)-  (CA INDEX NAME)
```

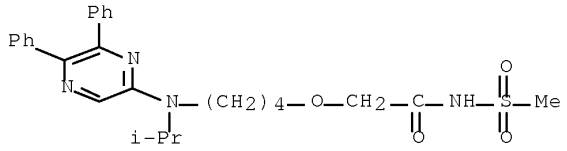


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:701355 HCAPLUS Full-text
DOCUMENT NUMBER: 156:646641
TITLE: Hair growth stimulants containing pyrazine compounds
INVENTOR(S): Todo, Makoto
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2012092079	A	20120517	JP 2010-242887	20101029

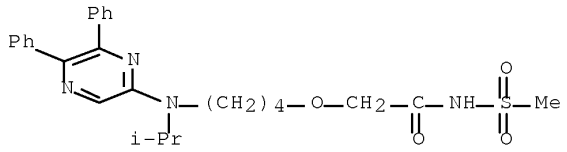
PRIORITY APPLN. INFO.: JP 2010-242887 20101029
OTHER SOURCE(S): MARPAT 156:646641
IT 475086-01-2
RL: BSU (Biological study, unclassified); COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(hair growth stimulants containing diphenylpyrazine compds.)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



L7 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:495189 HCAPLUS Full-text
DOCUMENT NUMBER: 156:469991
TITLE: Compounds capable of modulating/preserving endothelial integrity for use in prevention or treatment of acute traumatic coagulopathy and resuscitated cardiac arrest
INVENTOR(S): Johansson, Paer; Ostrowski, Sisse Rye
PATENT ASSIGNEE(S): Rigshospitalet, Den.
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

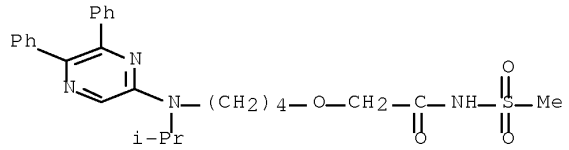
WO 2012041334 A1 20120405 WO 2011-DK50375 20110930
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: DK 2010-70427 A 20101001
IT 475086-01-2
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostacyclin related compds. capable of modulating or preserving endothelial integrity for use in prevention or treatment of acute traumatic coagulopathy and resuscitated cardiac arrest)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:36836 HCAPLUS Full-text
DOCUMENT NUMBER: 157:184254
TITLE: Therapeutic targets for pulmonary hypertension
AUTHOR(S): Sorbera, L. A.; Rajendran, S.; Dulsat, C.; Forns, N.; Rosa, E.
CORPORATE SOURCE: Thomson Reuters, Barcelona, Spain
SOURCE: Drugs of the Future (2010), 35(11), 947-954
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT 475086-01-2, Selexipag
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identifying novel target may be effective in treatment of patient with pulmonary hypertension)
RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



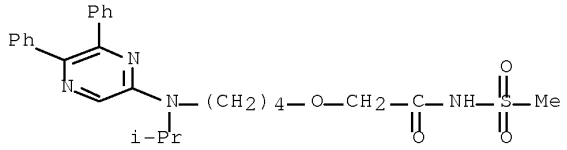
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1399337 HCAPLUS Full-text
DOCUMENT NUMBER: 155:607009
TITLE: Methods of treatment of patients at increased risk of development of ischemic events and compounds hereof
INVENTOR(S): Johansson, Paer
PATENT ASSIGNEE(S): Thrombologic APS, Den.
SOURCE: PCT Int. Appl., 60pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011134478	A2	20111103	WO 2011-DK50142	20110429
WO 2011134478	A3	20111215		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: DK 2010-70181 A 20100429
IT 475086-01-2
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treatment of patients at increased risk of developing ischemic events)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



L7 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:262241 HCAPLUS Full-text
DOCUMENT NUMBER: 154:292447
TITLE: Base addition salts of 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide, and use thereof
INVENTOR(S): Victor, M. Diaz Perez; Jennifer, Hill
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011024874	A1	20110303	WO 2010-JP64416	20100825

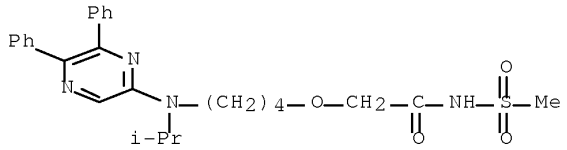
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.:
JP 2009-196079 A 20090826
JP 2009-196080 A 20090826
JP 2009-196081 A 20090826
JP 2009-196082 A 20090826

IT 1267423-47-1P 1267423-49-3P 1267423-51-7P
1267423-56-2P
RL: PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(base addition salts of 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide, and use thereof)
RN 1267423-47-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, compd. with 2-methyl-2-propanamine (1:1) (CA INDEX NAME)

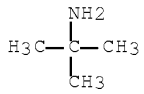
CM 1

CRN 475086-01-2
CMF C26 H32 N4 O4 S

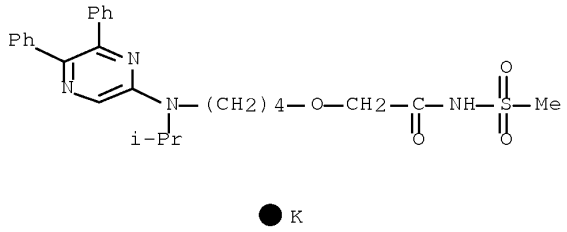


CM 2

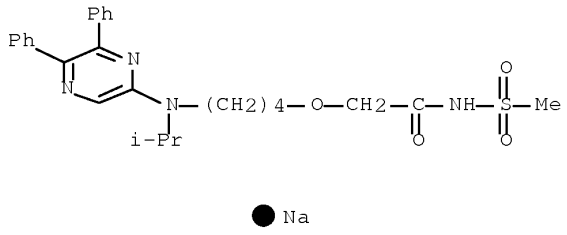
CRN 75-64-9
CMF C4 H11 N



RN 1267423-49-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, potassium salt (1:1) (CA INDEX NAME)



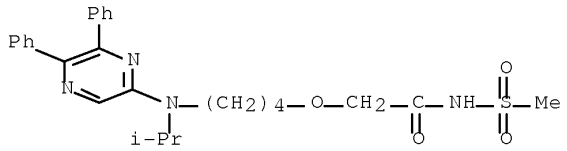
RN 1267423-51-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, sodium salt (1:1) (CA INDEX NAME)



RN 1267423-56-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)-, compd. with 2-(dimethylamino)ethanol (1:1) (CA INDEX NAME)

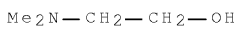
CM 1

CRN 475086-01-2
CMF C26 H32 N4 O4 S

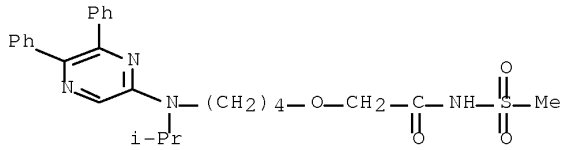


CM 2

CRN 108-01-0
CMF C4 H11 N O



IT 475086-01-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of base addition salts of 2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}-N-(methylsulfonyl)acetamide, and use thereof)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:174252 HCAPLUS Full-text
DOCUMENT NUMBER: 154:225444
TITLE: Substituted diphenylpyrazine derivatives
INVENTOR(S): Harbeson, Scott L.; Masse, Craig E.; Liu, Julie F.
PATENT ASSIGNEE(S): Concert Pharmaceuticals, Inc., USA

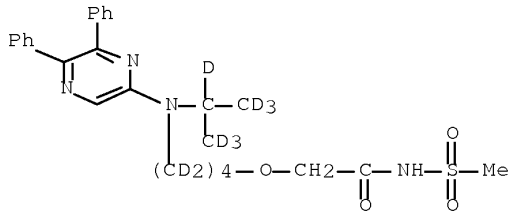
SOURCE: PCT Int. Appl., 51pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011017612	A1	20110210	WO 2010-US44704	20100806

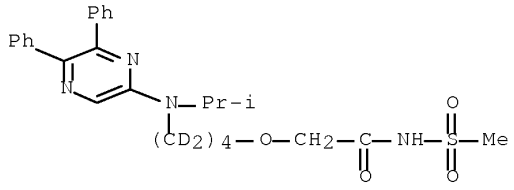
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,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

RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

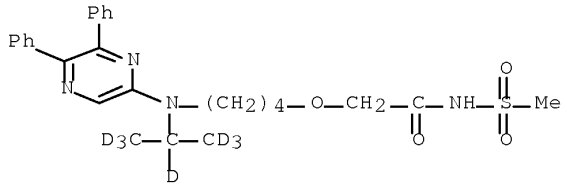
PRIORITY APPLN. INFO.: US 2009-231878P P 20090806
OTHER SOURCE(S): CASREACT 154:225444; MARPAT 154:225444
IT 1265295-11-1P 1265295-16-6P 1265295-21-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(diphenylpyrazine derivs. as PGI2 receptor agonists)
RN 1265295-11-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methylsulfonyl)- (CA INDEX NAME)



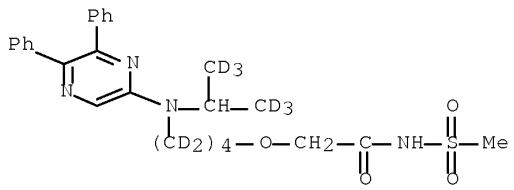
RN 1265295-16-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methylsulfonyl)- (CA INDEX NAME)



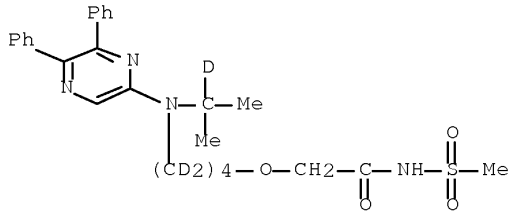
RN 1265295-21-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



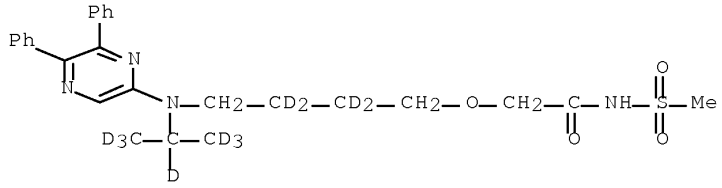
IT 1265295-58-6 1265295-59-7 1265295-60-0
1265295-61-1 1265295-62-2 1265295-63-3
1265295-64-4 1265295-65-5 1265295-66-6
1265295-67-7 1265295-68-8 1265295-69-9
1265295-70-2 1265295-71-3 1265295-72-4
1265295-73-5 1265295-74-6 1265295-75-7
1265295-76-8 1265295-77-9 1265295-78-0
1265295-79-1 1265295-80-4 1265295-81-5
1265295-82-6 1265295-83-7 1265295-84-8
1265295-85-9 1265295-86-0 1265295-87-1
1265295-88-2 1265295-89-3 1265295-90-6
1265295-91-7 1265295-92-8 1265295-93-9
1265295-94-0 1265295-95-1 1265295-96-2
1265295-97-3 1265295-99-5 1265296-00-1
1265296-01-2 1265296-02-3 1265296-03-4
1265296-05-6 1265296-06-7 1265296-07-8
1265296-08-9 1265296-09-0 1265296-10-3
1265296-11-4 1265296-12-5 1265296-13-6
1265296-14-7 1265296-15-8 1265296-16-9
1265296-17-0 1265296-18-1 1265296-19-2
1265296-20-5 1265296-21-6 1265296-22-7
1265296-23-8 1265296-24-9 1265296-25-0
1265296-26-1 1265296-27-2 1265296-28-3
1265296-29-4 1265296-30-7 1265296-31-8
1265296-32-9 1265296-33-0 1265296-34-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphenylpyrazine derivs. as PGI2 receptor agonists)
RN 1265295-58-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methylsulfonyl)- (CA INDEX NAME)



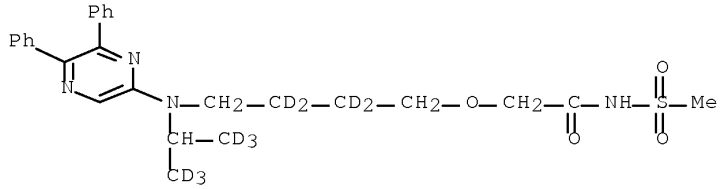
RN 1265295-59-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methylsulfonyl)- (CA INDEX NAME)



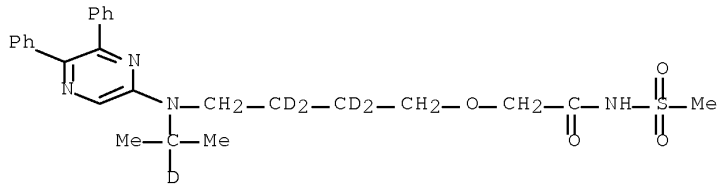
RN 1265295-60-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



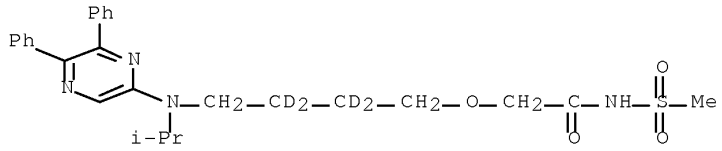
RN 1265295-61-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-2,2,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



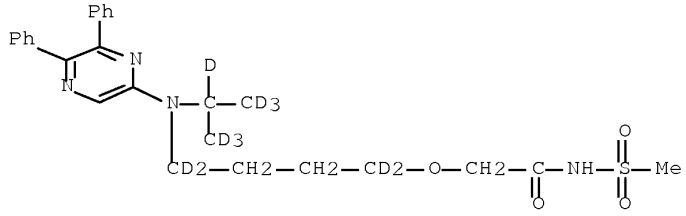
RN 1265295-62-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



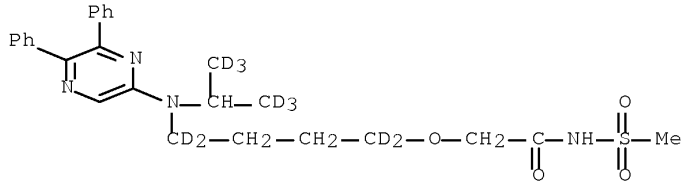
RN 1265295-63-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



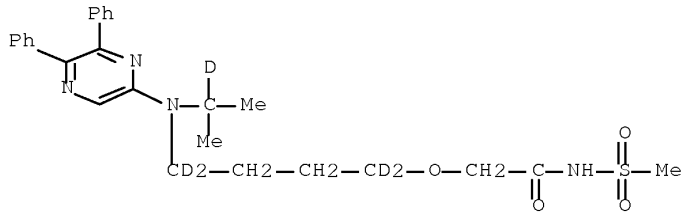
RN 1265295-64-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



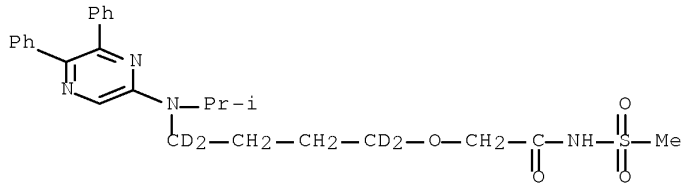
RN 1265295-65-5 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



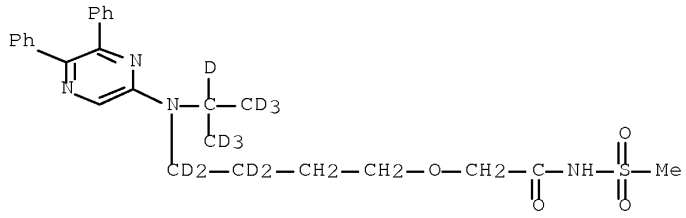
RN 1265295-66-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



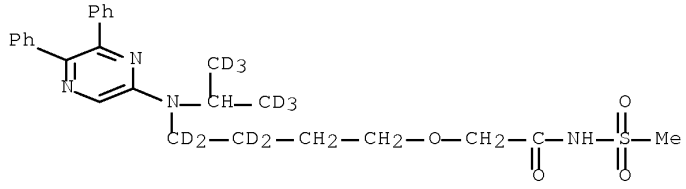
RN 1265295-67-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



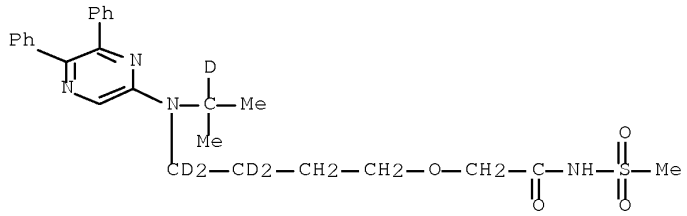
RN 1265295-68-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-3,3,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



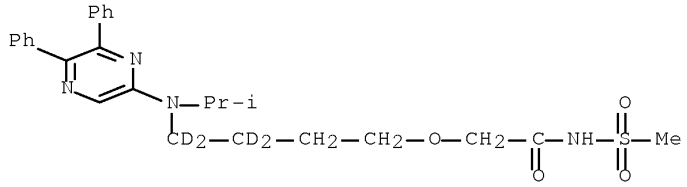
RN 1265295-69-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-3,3,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



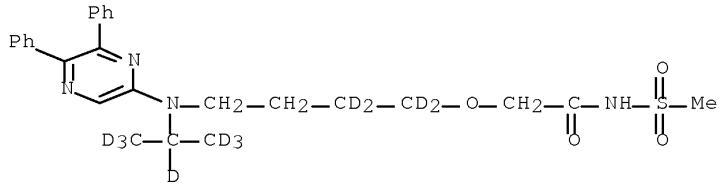
RN 1265295-70-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-3,3,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



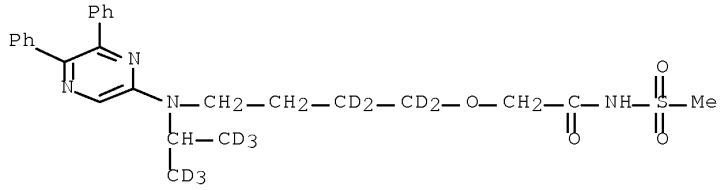
RN 1265295-71-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-3,3,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



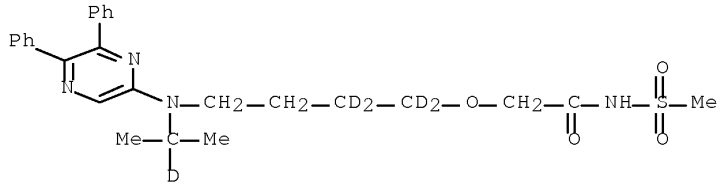
RN 1265295-72-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



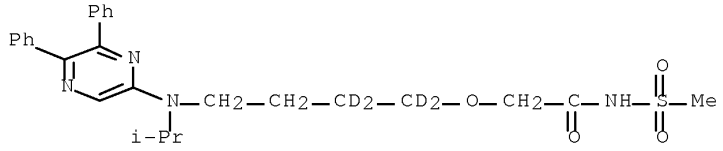
RN 1265295-73-5 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



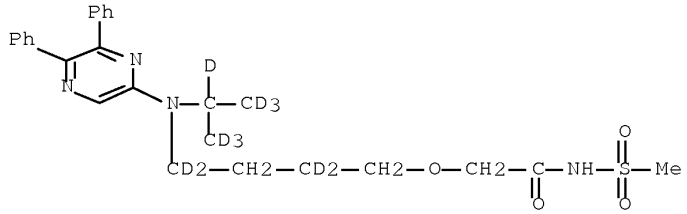
RN 1265295-74-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



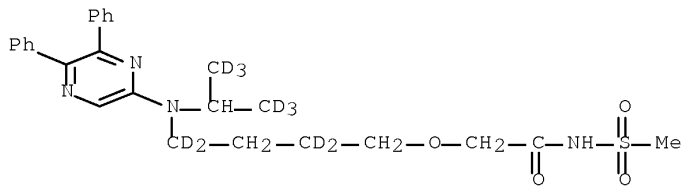
RN 1265295-75-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



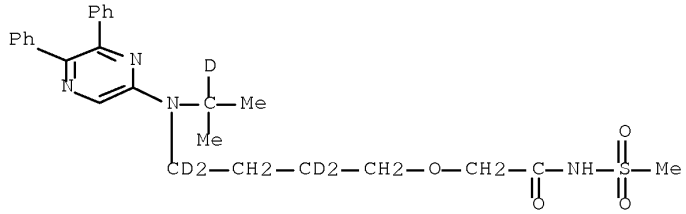
RN 1265295-76-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



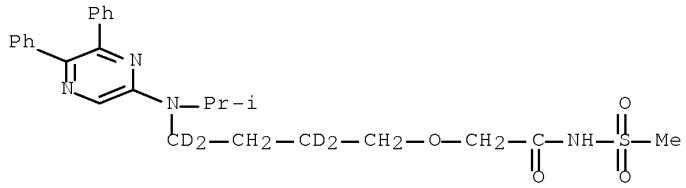
RN 1265295-77-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-2,2,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



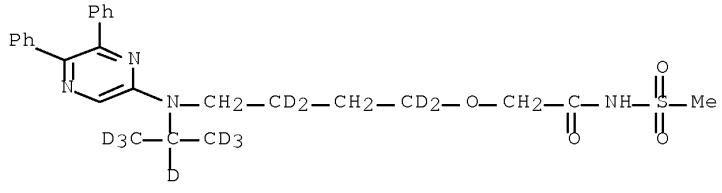
RN 1265295-78-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



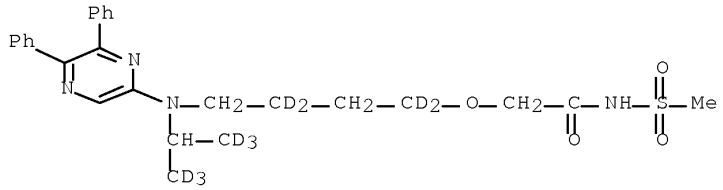
RN 1265295-79-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,4,4-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



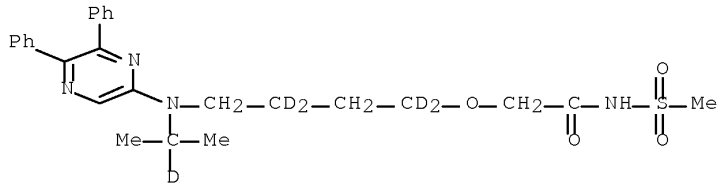
RN 1265295-80-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



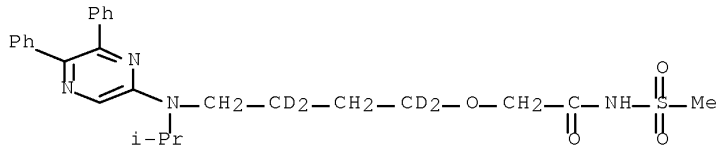
RN 1265295-81-5 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



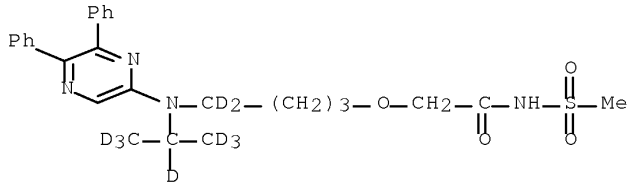
RN 1265295-82-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



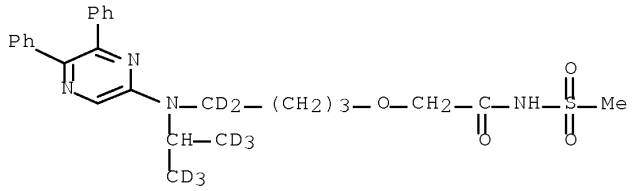
RN 1265295-83-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,3,3-d4]-N-(methylsulfonyl)- (CA INDEX NAME)



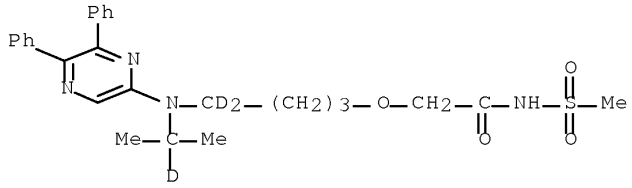
RN 1265295-84-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-4,4-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



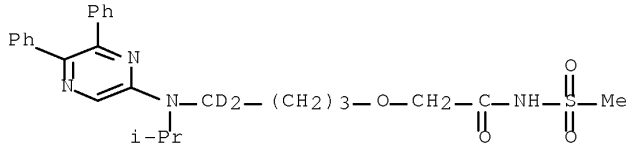
RN 1265295-85-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-4,4-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



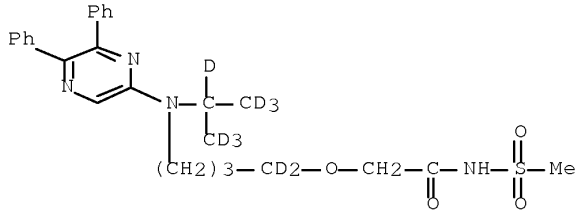
RN 1265295-86-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-4,4-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



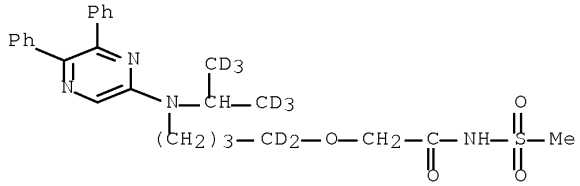
RN 1265295-87-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-4,4-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



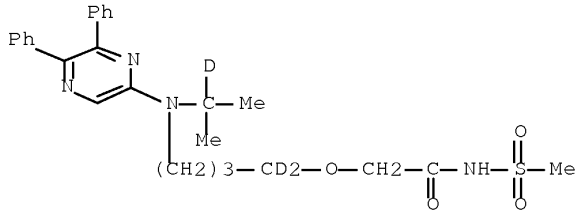
RN 1265295-88-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



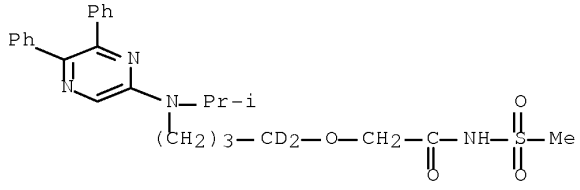
RN 1265295-89-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1-d2]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 1265295-90-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1-d2]-N-(methylsulfonyl)- (CA INDEX NAME)

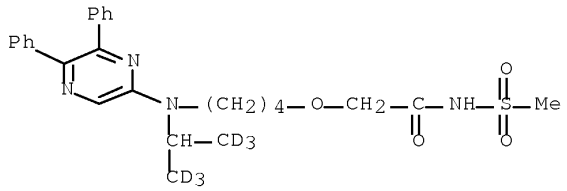


RN 1265295-91-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1-d2]-N-(methylsulfonyl)- (CA INDEX NAME)

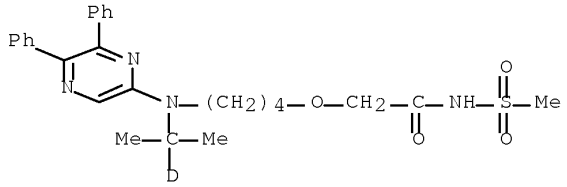


RN 1265295-92-8 HCAPLUS

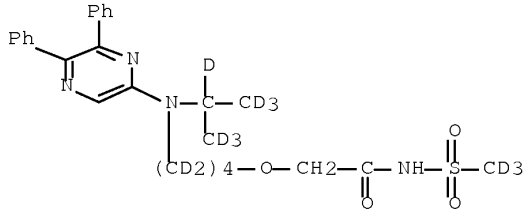
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



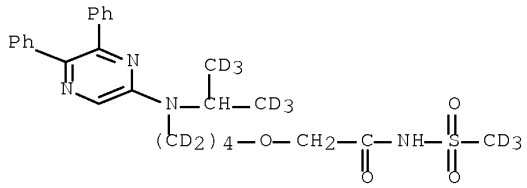
RN 1265295-93-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



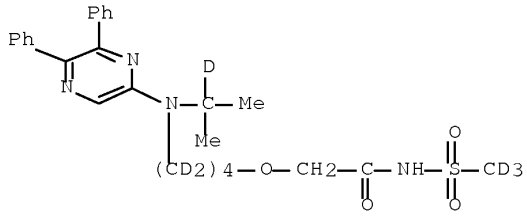
RN 1265295-94-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



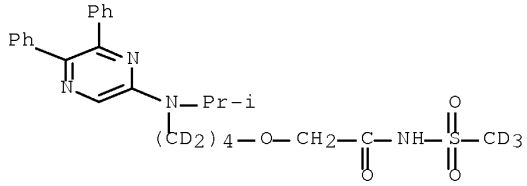
RN 1265295-95-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



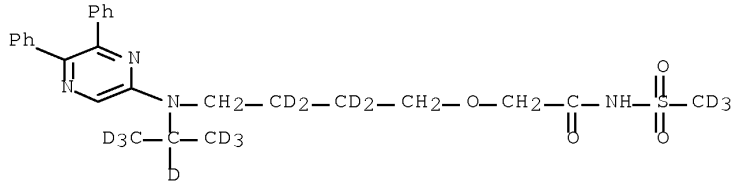
RN 1265295-96-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



RN 1265295-97-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2,3,3,4,4-d8]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)

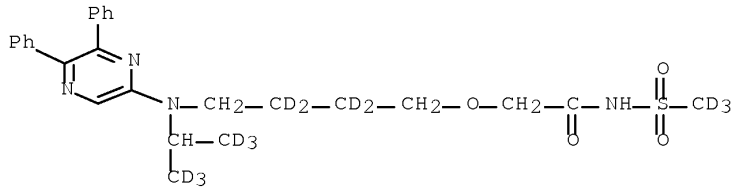


RN 1265295-99-5 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)

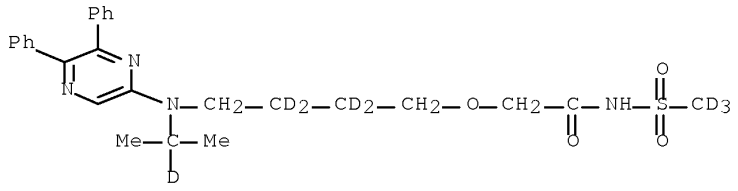


RN 1265296-00-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-

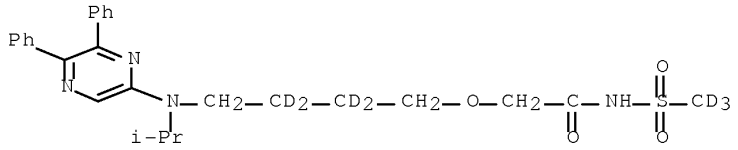
d3]amino]butoxy-2,2,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



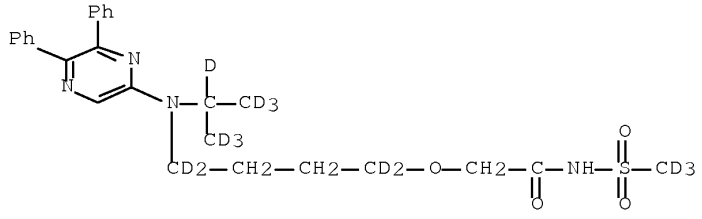
RN 1265296-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



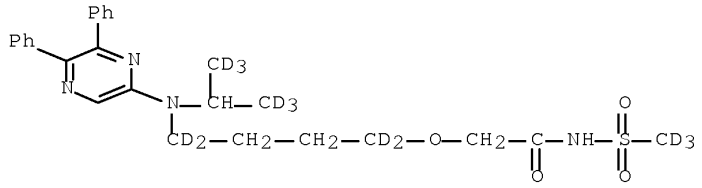
RN 1265296-02-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



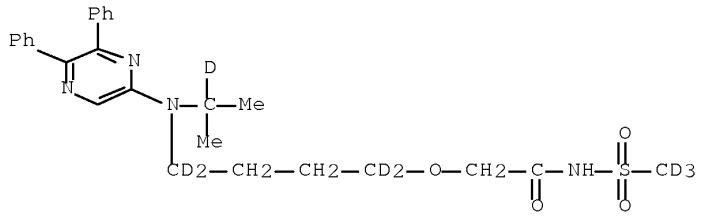
RN 1265296-03-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



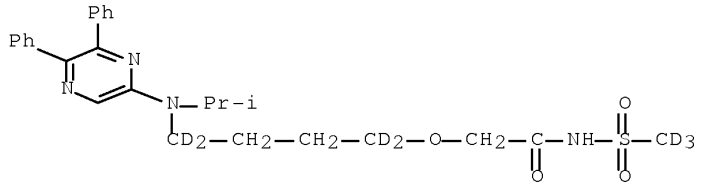
RN 1265296-05-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



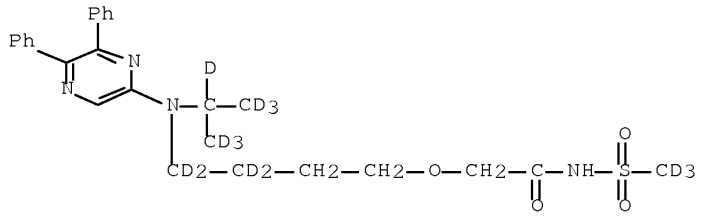
RN 1265296-06-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



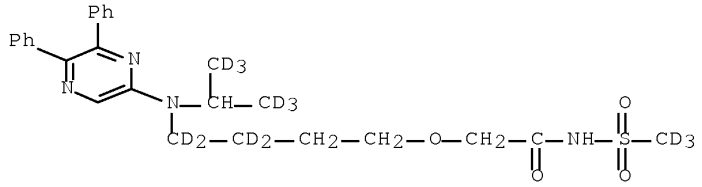
RN 1265296-07-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



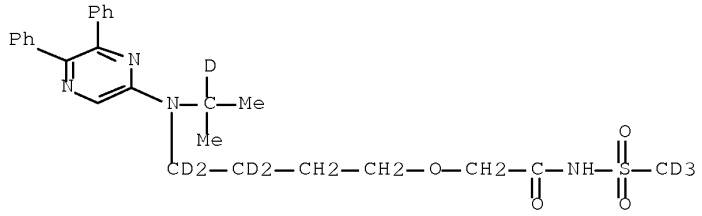
RN 1265296-08-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-3,3,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



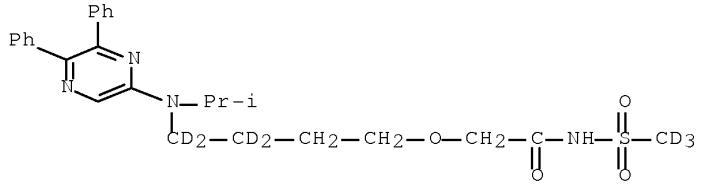
RN 1265296-09-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-3,3,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



RN 1265296-10-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-3,3,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)

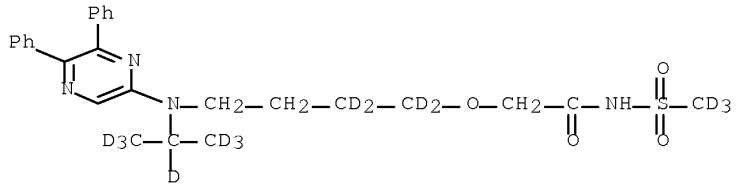


RN 1265296-11-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-3,3,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)

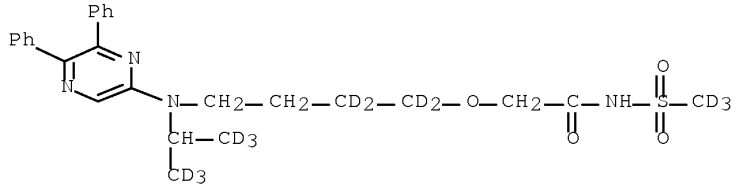


RN 1265296-12-5 HCAPLUS

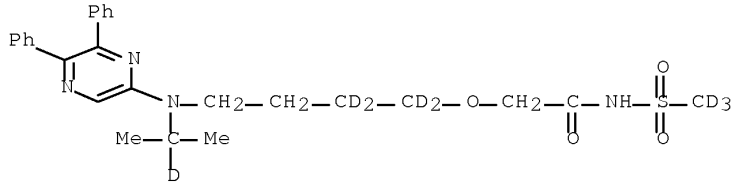
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



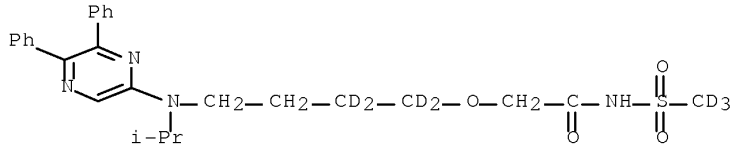
RN 1265296-13-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



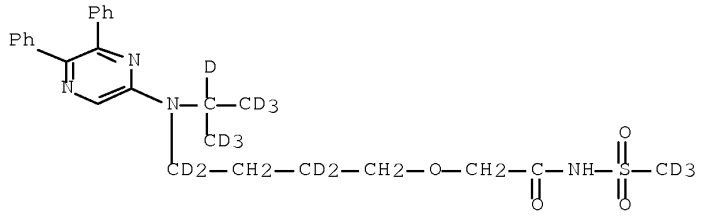
RN 1265296-14-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



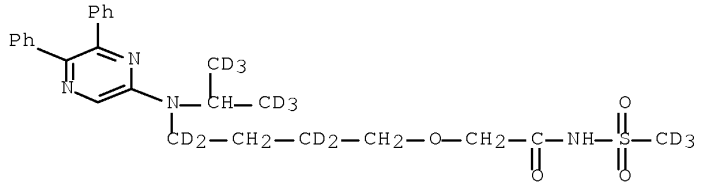
RN 1265296-15-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



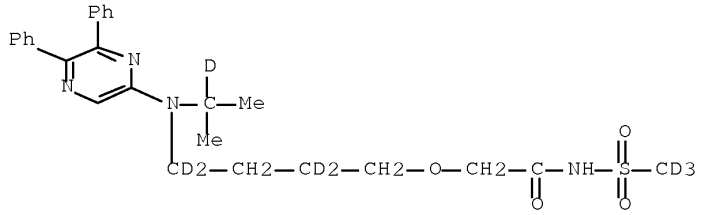
RN 1265296-16-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



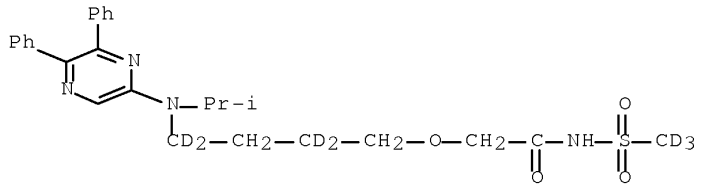
RN 1265296-17-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-2,2,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



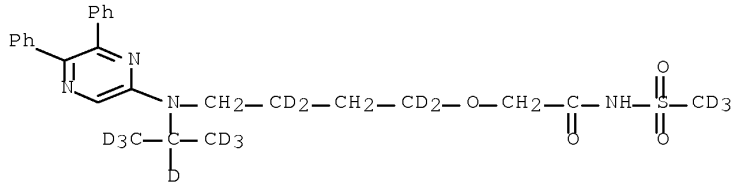
RN 1265296-18-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



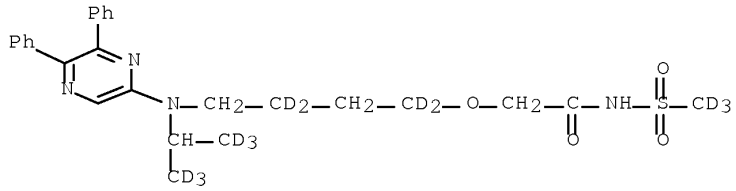
RN 1265296-19-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,4,4-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



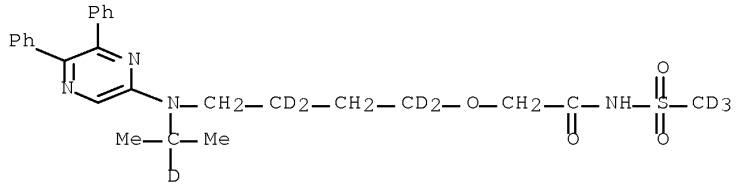
RN 1265296-20-5 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



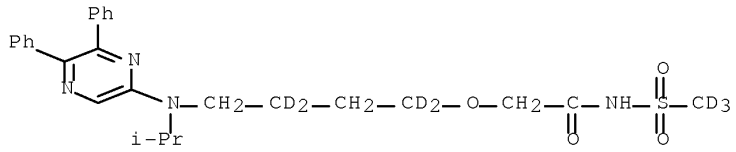
RN 1265296-21-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



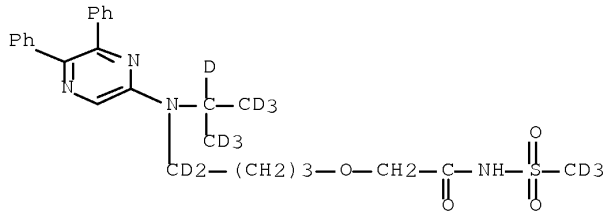
RN 1265296-22-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



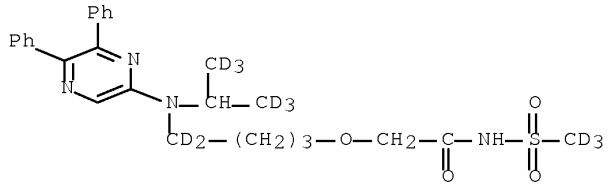
RN 1265296-23-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,3,3-d4]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



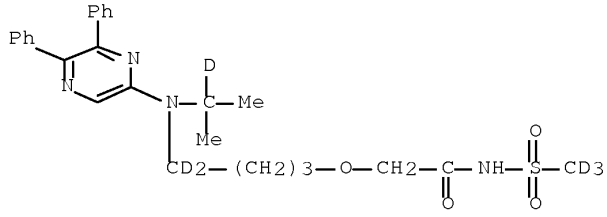
RN 1265296-24-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-4,4-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



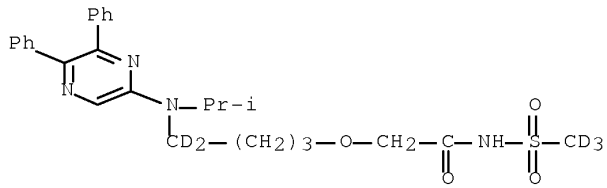
RN 1265296-25-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-4,4-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



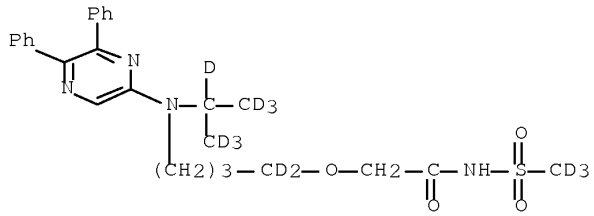
RN 1265296-26-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-4,4-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



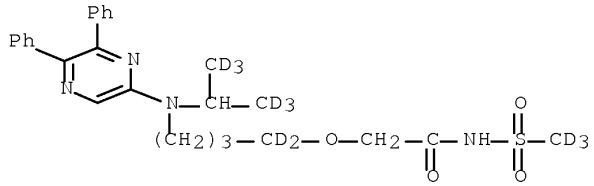
RN 1265296-27-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-4,4-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



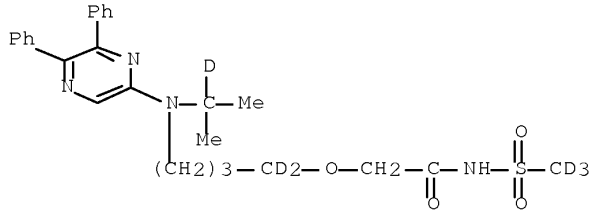
RN 1265296-28-3 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



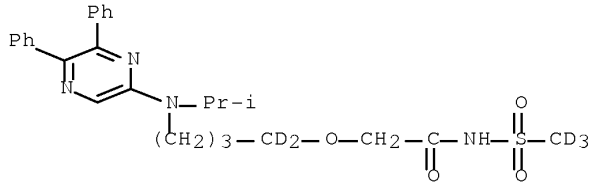
RN 1265296-29-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



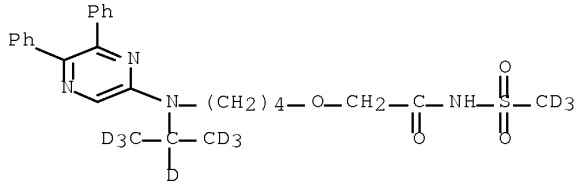
RN 1265296-30-7 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



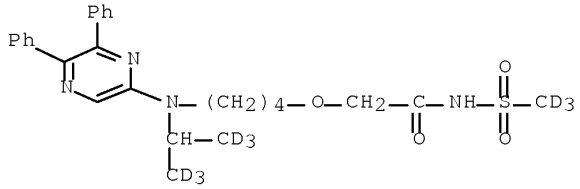
RN 1265296-31-8 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1-d2]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



RN 1265296-32-9 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)

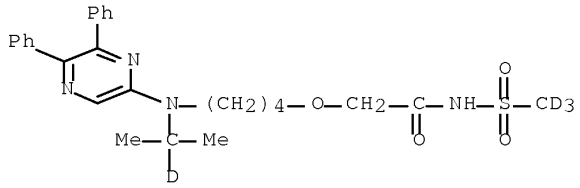


RN 1265296-33-0 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



RN 1265296-34-1 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-

d)amino]butoxy]-N-(methyl-d3-sulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1630353 HCAPLUS Full-text
DOCUMENT NUMBER: 154:73139
TITLE: Crystals of PGI2 receptor agonistic agents, and use thereof
INVENTOR(S): Itou, Hideyuki; Nakamichi, Koji; Tosaka, Takashi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 40pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010150865	A1	20101229	WO 2010-JP60798	20100625
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2764475	A1	20101229	CA 2010-2764475	20100625
AR 77242	A1	20110810	AR 2010-102270	20100625
AU 2010263569	A1	20120202	AU 2010-263569	20100625
EP 2447254	A1	20120502	EP 2010-792183	20100625
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR				
CN 102459198	A	20120516	CN 2010-80028176	20100625
KR 2012109457	A	20121008	KR 2012-7000526	20100625
ZA 2011009099	A	20120829	ZA 2011-9099	20111209
MX 2011013471	A	20120130	MX 2011-13471	20111213
US 20120101276	A1	20120426	US 2011-379531	20111220

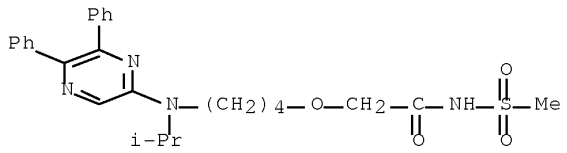
PRIORITY APPLN. INFO.: JP 2009-151727 A 20090626
JP 2009-151728 A 20090626
JP 2009-151729 A 20090626
WO 2010-JP60798 W 20100625

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 475086-01-2P
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(crystals of PGI2 receptor agonistic agents, and use thereof)

RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1251056 HCAPLUS Full-text

DOCUMENT NUMBER: 155:1448

TITLE: Selexipag: a selective prostacyclin receptor agonist that does not affect rat gastric function

AUTHOR(S): Morrison, Keith; Ernst, Roland; Hess, Patrick; Studer, Rolf; Clozel, Martine

CORPORATE SOURCE: Drug Discovery Department, Actelion Pharmaceuticals Ltd, Allschwil, Switz.

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2010), 335(1), 249-255
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

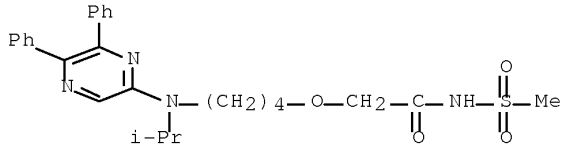
DOCUMENT TYPE: Journal

LANGUAGE: English

IT 475086-01-2, Selexipag
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective prostacyclin receptor agonist selexipag did not alter gastric function of rat)

RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:845010 HCAPLUS Full-text
DOCUMENT NUMBER: 153:164406
TITLE: Methods of identifying critically ill patients at increased risk of development of organ failure and compounds for the treatment hereof
INVENTOR(S): Johansson, Paer
PATENT ASSIGNEE(S): Thrombologic APS, Den.
SOURCE: PCT Int. Appl., 90pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010075861	A2	20100708	WO 2009-DK50357	20091230
WO 2010075861	A3	20101007		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
CA 2747310	A1	20100708	CA 2009-2747310	20091230
AU 2009335398	A1	20110721	AU 2009-335398	20091230
KR 2011115578	A	20111021	KR 2011-7017937	20091230
EP 2384196	A2	20111109	EP 2009-801149	20091230
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS				
CN 102271685	A	20111207	CN 2009-80153297	20091230
JP 2012514014	T	20120621	JP 2011-543978	20091230
ZA 2011004357	A	20120829	ZA 2011-4357	20091230
MX 2011006995	A	20110927	MX 2011-6995	20110628
US 20110268732	A1	20111103	US 2011-142935	20110630
PRIORITY APPLN. INFO.:			DK 2008-1844 A	20081230
			US 2009-161487P P	20090319

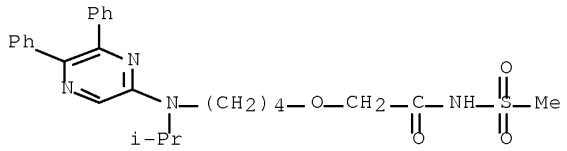
WO 2009-DK50357 W 20091230

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 475086-01-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of identifying critically ill patients at increased risk of development of organ failure and compds. for treatment hereof)

RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L7 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:214047 HCAPLUS Full-text

DOCUMENT NUMBER: 152:271363

TITLE: Therapeutic compositions containing macitentan and prostacyclin receptor agonists

INVENTOR(S): Clozel, Martine

PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.

SOURCE: PCT Int. Appl., 13pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

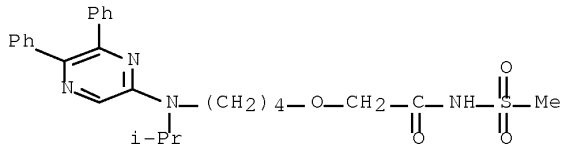
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010018549	A2	20100218	WO 2009-IB53553	20090812
WO 2010018549	A3	20100729		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2009280843	A1	20100218	AU 2009-280843	20090812
CA 2731370	A1	20100218	CA 2009-2731370	20090812
AR 73031	A1	20101006	AR 2009-103113	20090812
KR 2011045006	A	20110503	KR 2011-7003547	20090812
EP 2315587	A2	20110504	EP 2009-786912	20090812

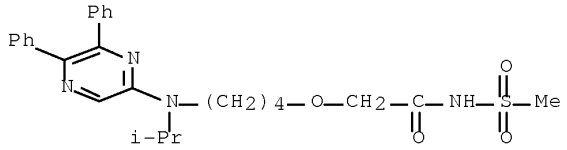
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS

CN 102099026	A	20110615	CN 2009-80127993		20090812
CN 102099026	B	20120829			
JP 2011530581	T	20111222	JP 2011-522608		20090812
MX 2011001625	A	20110329	MX 2011-1625		20110211
US 20110136818	A1	20110609	US 2011-58639		20110211
IN 2011CN01623	A	20111202	IN 2011-CN1623		20110308
ZA 2011001900	A	20120829	ZA 2011-1900		20110311
PRIORITY APPLN. INFO.:			WO 2008-IB53252	A	20080813
			WO 2009-IB53553	W	20090812

IT 475086-01-2 475086-01-2D, salts
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NS-304; therapeutic compns. containing macitentan and prostacyclin receptor agonists)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



L7 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:111452 HCAPLUS Full-text
DOCUMENT NUMBER: 152:184324
TITLE: Therapeutic agent for chronic renal failure
INVENTOR(S): Matsuda, Fuko; Iseki, Katsuhiko; Kurumatani, Hajimu; Miyamoto, Mitsuko
PATENT ASSIGNEE(S): Toray Industries, Inc., Japan
SOURCE: PCT Int. Appl., 39pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010010909	A1	20100128	WO 2009-JP63153	20090723
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2730599	A1	20100128	CA 2009-2730599	20090723
EP 2305653	A1	20110406	EP 2009-800423	20090723
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS				
KR 2011036572	A	20110407	KR 2011-7000559	20090723
CN 102105453	A	20110622	CN 2009-80128581	20090723
MX 2011000897	A	20110330	MX 2011-897	20110121
IN 2011KN00361	A	20111125	IN 2011-KN361	20110124
US 20110178103	A1	20110721	US 2011-55242	20110330
PRIORITY APPLN. INFO.:			JP 2008-190085 A	20080723
			WO 2009-JP63153 W	20090723

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

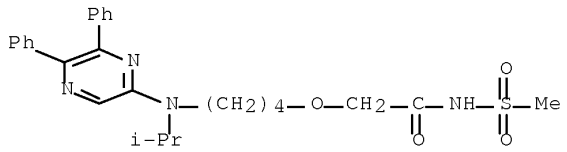
OTHER SOURCE(S): MARPAT 152:184324

IT 475086-01-2

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic agent for chronic renal failure)

RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1618864 HCAPLUS Full-text

DOCUMENT NUMBER: 152:67647

TITLE: Therapeutic agent for inflammatory bowel disease

INVENTOR(S): Kyoi, Takashi

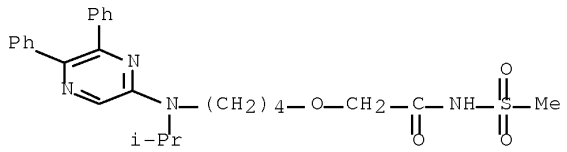
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan

SOURCE: PCT Int. Appl., 25pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

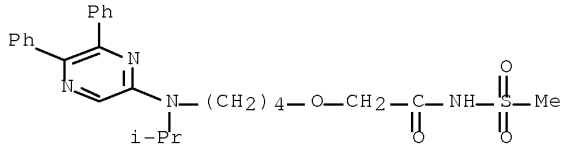
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157398	A1	20091230	WO 2009-JP61287	20090622
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2728161	A1	20091230	CA 2009-2728161	20090622
EP 2289518	A1	20110302	EP 2009-770108	20090622
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS				
KR 2011036537	A	20110407	KR 2010-7028238	20090622
CN 102065864	A	20110518	CN 2009-80124684	20090622
CN 102065864	B	20121121		
US 20110118254	A1	20110519	US 2010-791	20101222

PRIORITY APPLN. INFO.: JP 2008-162640 A 20080623
WO 2009-JP61287 W 20090622

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 152:67647
IT 475086-01-2 475086-01-2D, salt
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for inflammatory bowel disease)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



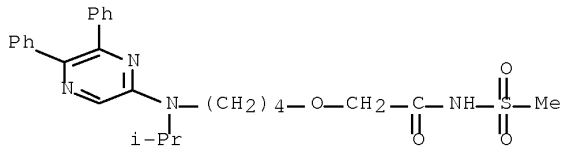
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1618854 HCAPLUS Full-text
DOCUMENT NUMBER: 152:67646
TITLE: Therapeutic agent for intestinal tract injury accompanying administration of a non-steroid anti-inflammatory agent
INVENTOR(S): Kyoi, Takashi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

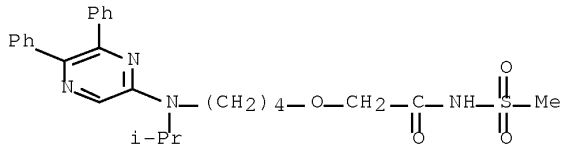
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157397	A1	20091230	WO 2009-JP61286	20090622

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-162639 A 20080623
OTHER SOURCE(S): MARPAT 152:67646
IT 475086-01-2 475086-01-2D, salt
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for intestinal tract injury accompanying administration of a non-steroid anti-inflammatory agents)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

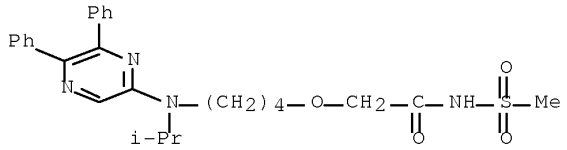
L7 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1618851 HCAPLUS Full-text
DOCUMENT NUMBER: 152:67707
TITLE: Therapeutic agent for spinal canal stenosis
INVENTOR(S): Kuwano, Keiichi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157396	A1	20091230	WO 2009-JP61285	20090622
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2728089	A1	20091230	CA 2009-2728089	20090622
EP 2292231	A1	20110309	EP 2009-770106	20090622
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,				

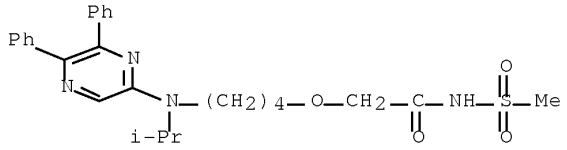
IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS

KR 2011033125	A	20110330	KR 2010-7027945		20090622
CN 102065863	A	20110518	CN 2009-80124683		20090622
US 20110105518	A1	20110505	US 2010-758		20101222
IN 2011CN00452	A	20111118	IN 2011-CN452		20110120
PRIORITY APPLN. INFO.:			JP 2008-162638	A	20080623
			WO 2009-JP61285	W	20090622

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 152:67707
IT 475086-01-2 475086-01-2D, salt
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for spinal canal stenosis)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT:	2	THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT:	11	THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER:	2009:1598176 HCAPLUS Full-text
DOCUMENT NUMBER:	152:67703
TITLE:	Therapeutic agent for erectile dysfunction
INVENTOR(S):	Higashioka, Masaya
PATENT ASSIGNEE(S):	Nippon Shinyaku Co., Ltd., Japan
SOURCE:	PCT Int. Appl., 23pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1

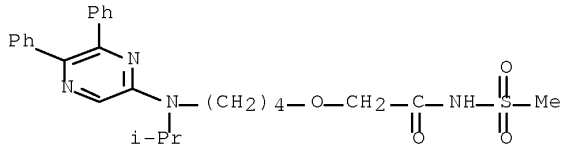
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009154246	A1	20091223	WO 2009-JP61071	20090618

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

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-160225 A 20080619
OTHER SOURCE(S): MARPAT 152:67703
IT 475086-01-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic agent for erectile dysfunction containing heterocyclic compds.)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1080888 HCAPLUS Full-text
DOCUMENT NUMBER: 151:305248
TITLE: Fibrosis inhibitor
INVENTOR(S): Murakami, Koji; Toramoto, Takuya
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009107736	A1	20090903	WO 2009-JP53582	20090226

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

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

AU 2009218115	A1	20090903	AU 2009-218115	20090226
CA 2716554	A1	20090903	CA 2009-2716554	20090226
EP 2246336	A1	20101103	EP 2009-714302	20090226
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS				
KR 2010135726	A	20101227	KR 2010-7018956	20090226
CN 101959868	A	20110126	CN 2009-80106979	20090226
MX 2010008745	A	20100830	MX 2010-8745	20100809
US 20110015211	A1	20110120	US 2010-919885	20100827
IN 2010CN05979	A	20110422	IN 2010-CN5979	20100922
PRIORITY APPLN. INFO.:			JP 2008-46999 A	20080228
			WO 2009-JP53582 W	20090226

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 151:305248

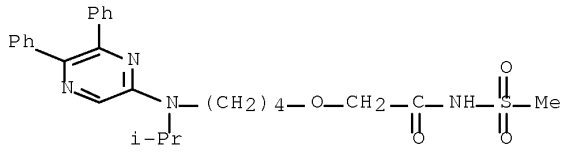
IT 475086-01-2 475086-01-2D, salts

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as fibrosis inhibitors)

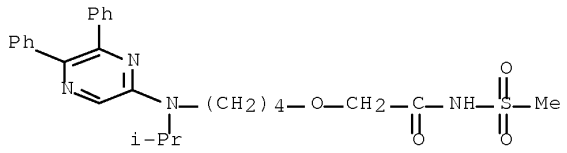
RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



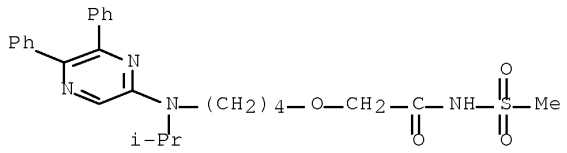
RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

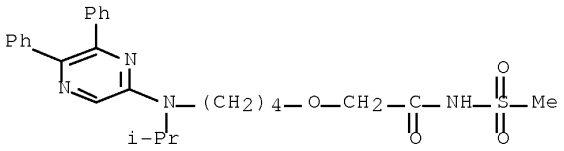
L7 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1059866 HCAPLUS Full-text
DOCUMENT NUMBER: 149:299321
TITLE: A long-acting and highly selective prostacyclin receptor agonist prodrug, 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide (NS-304), ameliorates rat pulmonary hypertension with unique relaxant responses of its active form, {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (MRE-269), on rat pulmonary artery
AUTHOR(S): Kuwano, Keiichi; Hashino, Asami; Noda, Kumiko; Kosugi, Keiji; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., Kisshoin, Minami-Ku, Kyoto, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2008), 326(3), 691-699
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475086-01-2, NS-304
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug NS-304 ameliorates pulmonary hypertension)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



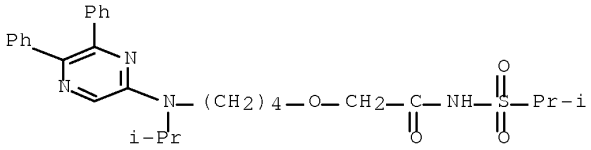
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:1195229 HCAPLUS Full-text
DOCUMENT NUMBER: 148:39274
TITLE: Synthesis and evaluation of N-acylsulfonamide and N-acylsulfonylurea prodrugs of a prostacyclin receptor agonist

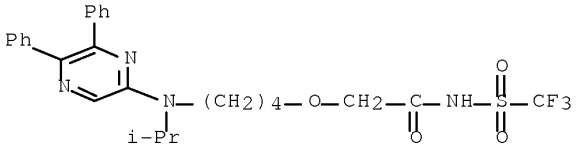
AUTHOR(S): Nakamura, Akio; Yamada, Tetsuhiro; Asaki, Tetsuo
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd, Kisshoin, Minami-Ku, Kyoto, 601 8550, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(24), 7720-7725
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:39274
IT 475086-01-2P 475086-03-4P 475086-05-6P
RL: PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-acylsulfonamide and N-acylsulfonylurea prodrugs of diphenylpyrazine prostacyclin receptor agonist)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



RN 475086-03-4 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-[(1-methylethyl)sulfonyl]- (CA INDEX NAME)



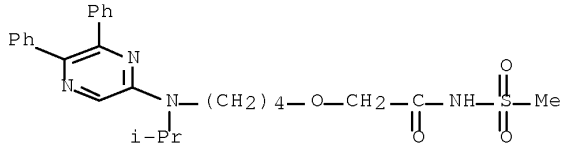
RN 475086-05-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-[(trifluoromethyl)sulfonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD

(3 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

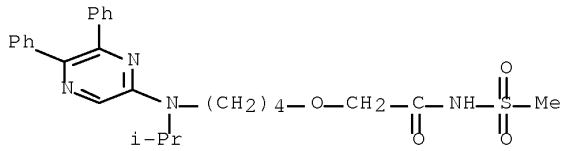
L7 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:1041397 HCAPLUS Full-text
DOCUMENT NUMBER: 147:514363
TITLE: Structure-activity studies on diphenylpyrazine derivatives: A novel class of prostacyclin receptor agonists
AUTHOR(S): Asaki, Tetsuo; Hamamoto, Taisuke; Sugiyama, Yukiteru; Kuwano, Keiichi; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., 14 Nishinosho-Monguchi-Cho, Kisshoin, Minami-ku, Kyoto, 601-8550, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(21), 6692-6704
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:514363
IT 475086-01-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity studies on diphenylpyrazine derivs., a class of prostacyclin receptor agonists)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:976851 HCAPLUS Full-text
DOCUMENT NUMBER: 147:461873
TITLE: 2-{4-[5,6-(Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl) acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug
AUTHOR(S): Kuwano, Keiichi; Hashino, Asami; Asaki, Tetsuo; Hamamoto, Taisuke; Yamada, Tetsuhiro; Okubo, Kaori; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2007), 322(3), 1181-1188
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475086-01-2P, NS 304
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(2-{4-[5,6-(Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl) acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug)
RN 475086-01-2 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)



OS.CITING REF COUNT: 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2002:849591 HCAPLUS Full-text
DOCUMENT NUMBER: 137:370112
TITLE: Preparation of derivatives of heterocyclic compounds such as pyridine, pyrimidine, 1,2,4-triazine, and pyrazine as antagonists of prostaglandin I2 receptor
INVENTOR(S): Asaki, Tetsuo; Hamamoto, Taisuke; Kuwano, Keiichi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088084	A1	20021107	WO 2002-JP4118	20020425

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

TW 316055	B	20091021	TW 2002-108440		20020424
CA 2445344	A1	20021107	CA 2002-2445344		20020425
CA 2445344	C	20110726			
AU 2002253588	A1	20021111	AU 2002-253588		20020425
EP 1400518	A1	20040324	EP 2002-722772		20020425
EP 1400518	B1	20070117			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2002009249	A	20040608	BR 2002-9249		20020425
CN 1516690	A	20040728	CN 2002-808977		20020425
CN 1301973	C	20070228			
RU 2283835	C2	20060920	RU 2003-134190		20020425
PT 1400518	E	20070330	PT 2002-722772		20020425
ES 2276931	T3	20070701	ES 2002-722772		20020425
KR 921760	B1	20091015	KR 2003-7014044		20020425
JP 4479152	B2	20100609	JP 2002-585386		20020425
US 20040102436	A1	20040527	US 2003-476196		20031023
US 7205302	B2	20070417			
MX 2003009800	A	20040129	MX 2003-9800		20031024
PRIORITY APPLN. INFO.:			JP 2001-129765	A	20010426
			WO 2002-JP4118	W	20020425

OTHER SOURCE(S): MARPAT 137:370112

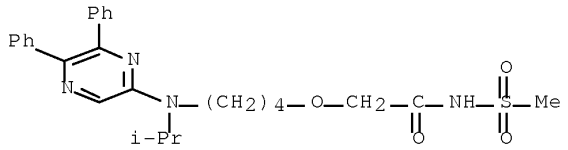
IT 475086-01-2P 475086-03-4P 475086-05-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of derivs. of heterocyclic compds. as antagonists of prostaglandin I2 receptor platelet aggregation inhibitor, or remedy for chronic artery obstruction, intermittent limping, or peripheral artery embolism)

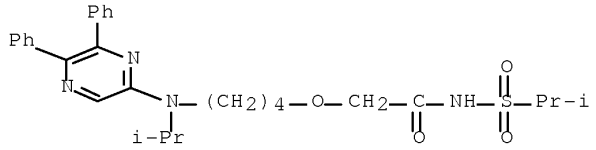
RN 475086-01-2 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-(methylsulfonyl)- (CA INDEX NAME)

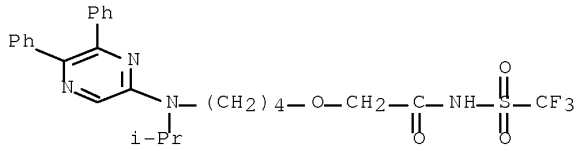


RN 475086-03-4 HCAPLUS

CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-[(1-methylethyl)sulfonyl]- (CA INDEX NAME)



RN 475086-05-6 HCAPLUS
CN Acetamide, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]-N-[(trifluoromethyl)sulfonyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l9 ibib hitstr 1-
YOU HAVE REQUESTED DATA FROM 20 ANSWERS - CONTINUE? Y/(N):y

L9 ANSWER 1 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1562497 HCAPLUS Full-text
DOCUMENT NUMBER: 157:624827
TITLE: Prostacyclin and analogs thereof administered during surgery for prevention and treatment of capillary leakage
INVENTOR(S): Johansson, Paer; Ostrowski, Sisse Rye
PATENT ASSIGNEE(S): Rigshospitalet, Den.
SOURCE: PCT Int. Appl., 70pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

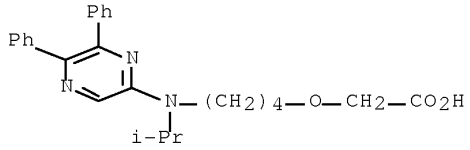
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012143012	A1	20121026	WO 2012-DK50100	20120330

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: DK 2011-70191 A 20110419
US 2011-476814P P 20110419

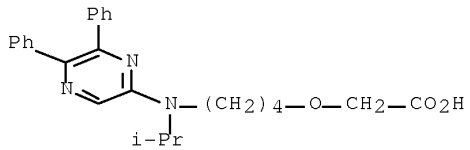
IT 475085-57-5
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(prostacyclin and analogs thereof administered during surgery for prevention and treatment of capillary leakage and effect on biomarker levels)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:1307001 HCAPLUS Full-text
DOCUMENT NUMBER: 157:400930
TITLE: Prostaglandins but not leukotrienes alter extracellular matrix protein deposition and cytokine release in primary human airway smooth muscle cells and fibroblasts
AUTHOR(S): Van Ly, David; Burgess, Janette K.; Brock, Thomas G.; Lee, Tak H.; Black, Judith L.; Oliver, Brian G. G.
CORPORATE SOURCE: Woolcock Institute of Medical Research, Sydney, Australia
SOURCE: American Journal of Physiology (2012), 303(2, Pt. 1), L239-L250
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475085-57-5, MRE-269
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prostaglandin but not leukotriene alteration of extracellular matrix protein deposition and cytokine release in primary human airway smooth muscle cells and fibroblasts)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)

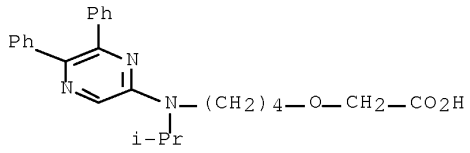


REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:701355 HCAPLUS Full-text
DOCUMENT NUMBER: 156:646641
TITLE: Hair growth stimulants containing pyrazine compounds
INVENTOR(S): Todo, Makoto
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 11pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2012092079	A	20120517	JP 2010-242887	20101029

PRIORITY APPLN. INFO.: JP 2010-242887 20101029
OTHER SOURCE(S): MARPAT 156:646641
IT 475085-57-5
RL: BSU (Biological study, unclassified); COS (Cosmetic use); BIOL (Biological study); USES (Uses)
(hair growth stimulants containing diphenylpyrazine compds.)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)

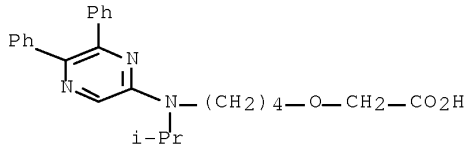


L9 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:495189 HCAPLUS Full-text
DOCUMENT NUMBER: 156:469991
TITLE: Compounds capable of modulating/preserving endothelial integrity for use in prevention or treatment of acute traumatic coagulopathy and resuscitated cardiac arrest
INVENTOR(S): Johansson, Paer; Ostrowski, Sisse Rye
PATENT ASSIGNEE(S): Rigshospitalet, Den.
SOURCE: PCT Int. Appl., 63pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012041334	A1	20120405	WO 2011-DK50375	20110930

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,

KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM,
ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD,
SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: DK 2010-70427 A 20101001
IT 475085-57-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostacyclin related compds. capable of modulating or preserving endothelial integrity for use in prevention or treatment of acute traumatic coagulopathy and resuscitated cardiac arrest)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



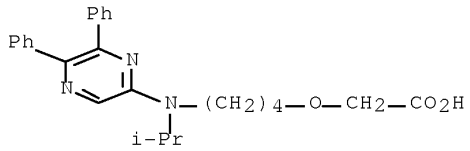
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1399337 HCAPLUS Full-text
DOCUMENT NUMBER: 155:607009
TITLE: Methods of treatment of patients at increased risk of development of ischemic events and compounds hereof
INVENTOR(S): Johansson, Paer
PATENT ASSIGNEE(S): Thrombologic APS, Den.
SOURCE: PCT Int. Appl., 60pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011134478	A2	20111103	WO 2011-DK50142	20110429
WO 2011134478	A3	20111215		

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,

MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL,
SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: DK 2010-70181 A 20100429
IT 475085-57-5
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of treatment of patients at increased risk of developing ischemic events)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



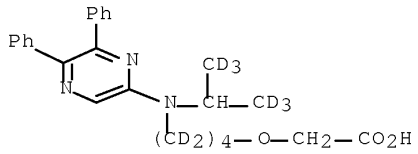
L9 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:174252 HCAPLUS Full-text
DOCUMENT NUMBER: 154:225444
TITLE: Substituted diphenylpyrazine derivatives
INVENTOR(S): Harbeson, Scott L.; Masse, Craig E.; Liu, Julie F.
PATENT ASSIGNEE(S): Concert Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 51pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011017612	A1	20110210	WO 2010-US44704	20100806

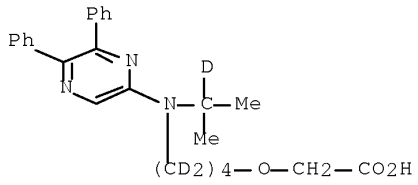
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP,
KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE,
SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ,
TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2009-231878P P 20090806
OTHER SOURCE(S): CASREACT 154:225444; MARPAT 154:225444

IT 1265295-22-4 1265295-23-5 1265295-24-6
1265295-25-7 1265295-26-8 1265295-27-9
1265295-28-0 1265295-29-1 1265295-30-4
1265295-31-5 1265295-32-6 1265295-33-7
1265295-34-8 1265295-35-9 1265295-36-0
1265295-37-1 1265295-38-2 1265295-39-3
1265295-40-6 1265295-41-7 1265295-42-8
1265295-43-9 1265295-44-0 1265295-45-1
1265295-46-2 1265295-47-3 1265295-48-4
1265295-49-5 1265295-50-8 1265295-51-9
1265295-52-0 1265295-53-1 1265295-54-2
1265295-55-3 1265295-56-4 1265295-57-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphenylpyrazine derivs. as PGI2 receptor agonists)

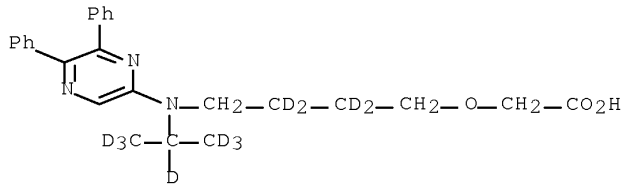
RN 1265295-22-4 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2,3,3,4,4-d8]- (CA INDEX NAME)



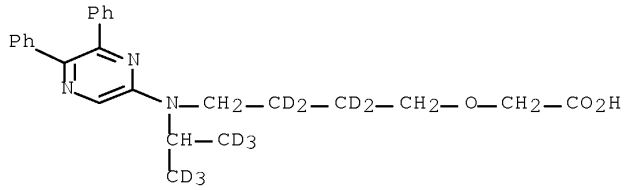
RN 1265295-23-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2,3,3,4,4-d8]- (CA INDEX NAME)



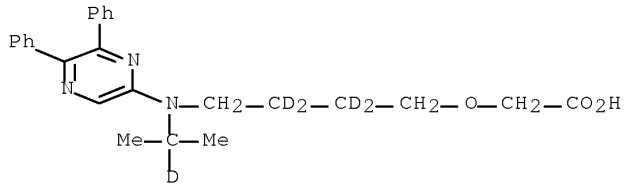
RN 1265295-24-6 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,3,3-d4]- (CA INDEX NAME)



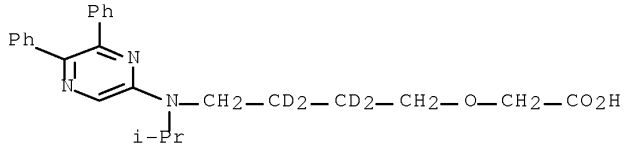
RN 1265295-25-7 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-2,2,3,3-d4]- (CA INDEX NAME)



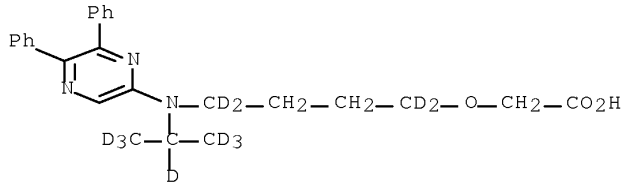
RN 1265295-26-8 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,3,3-d4]- (CA INDEX NAME)



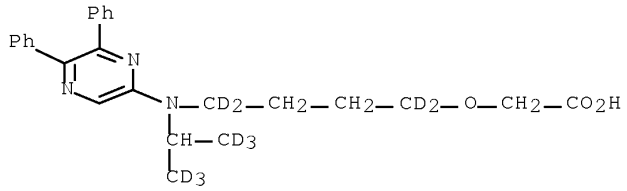
RN 1265295-27-9 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,3,3-d4]- (CA INDEX NAME)



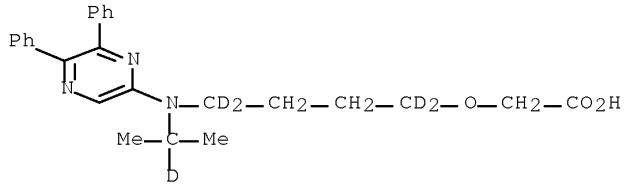
RN 1265295-28-0 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,4,4-d4]- (CA INDEX NAME)



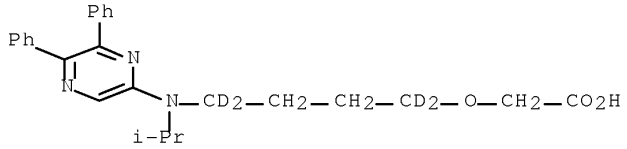
RN 1265295-29-1 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,4,4-d4]- (CA INDEX NAME)



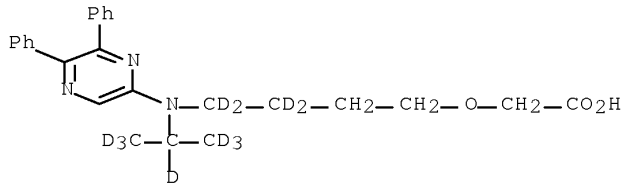
RN 1265295-30-4 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,4,4-d4]- (CA INDEX NAME)



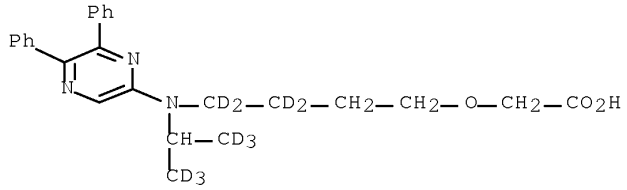
RN 1265295-31-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,4,4-d4]- (CA INDEX NAME)



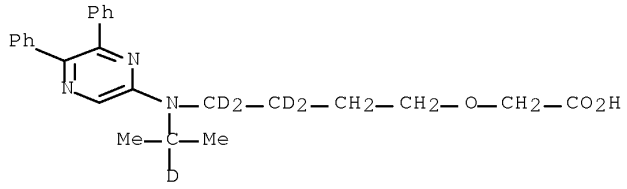
RN 1265295-32-6 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-3,3,4,4-d4]- (CA INDEX NAME)



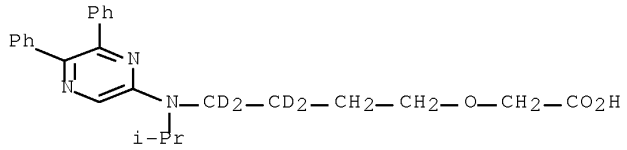
RN 1265295-33-7 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-3,3,4,4-d4]- (CA INDEX NAME)



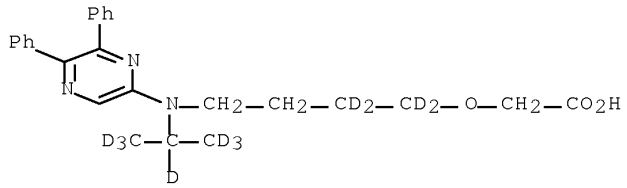
RN 1265295-34-8 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-3,3,4,4-d4]- (CA INDEX NAME)



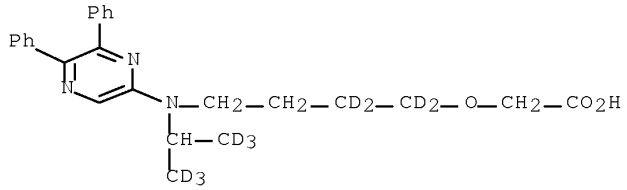
RN 1265295-35-9 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-3,3,4,4-d4]- (CA INDEX NAME)



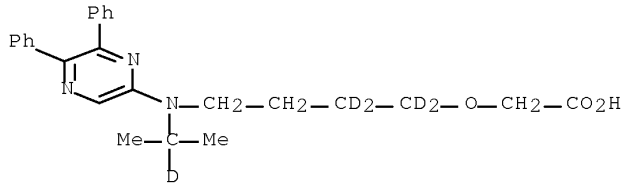
RN 1265295-36-0 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2-d4]- (CA INDEX NAME)



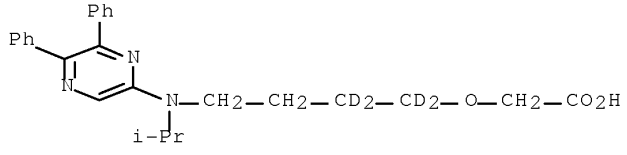
RN 1265295-37-1 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,2,2-d4]- (CA INDEX NAME)



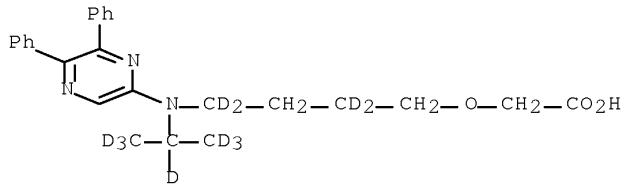
RN 1265295-38-2 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,2,2-d4]- (CA INDEX NAME)



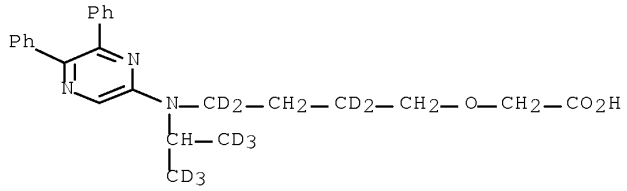
RN 1265295-39-3 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2-d4]- (CA INDEX NAME)



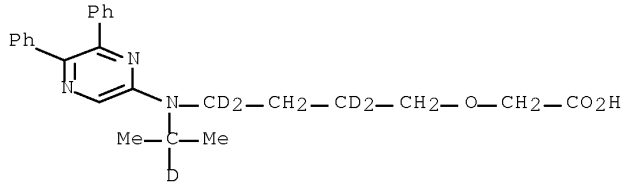
RN 1265295-40-6 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-2,2,4,4-d4]- (CA INDEX NAME)



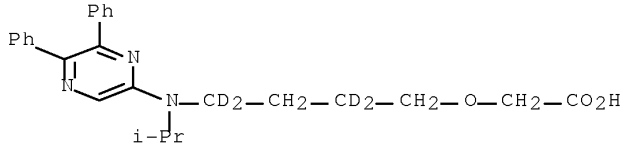
RN 1265295-41-7 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-2,2,4,4-d4]- (CA INDEX NAME)



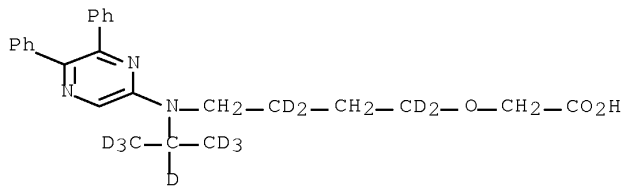
RN 1265295-42-8 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-2,2,4,4-d4]- (CA INDEX NAME)



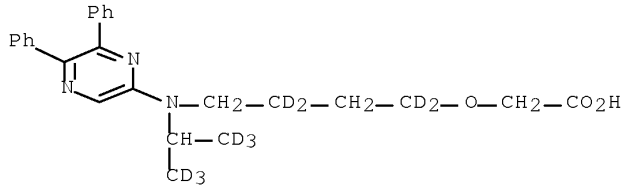
RN 1265295-43-9 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-2,2,4,4-d4]- (CA INDEX NAME)



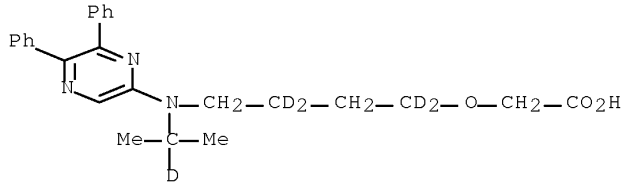
RN 1265295-44-0 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,3,3-d4]- (CA INDEX NAME)



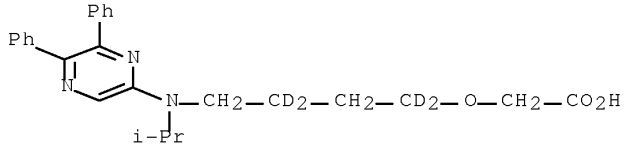
RN 1265295-45-1 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1,3,3-d4]- (CA INDEX NAME)



RN 1265295-46-2 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1,3,3-d4]- (CA INDEX NAME)

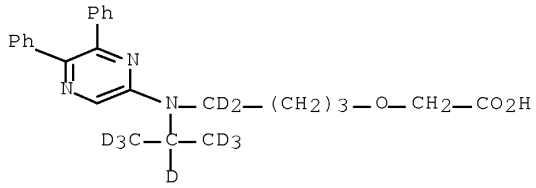


RN 1265295-47-3 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,3,3-d4]- (CA INDEX NAME)

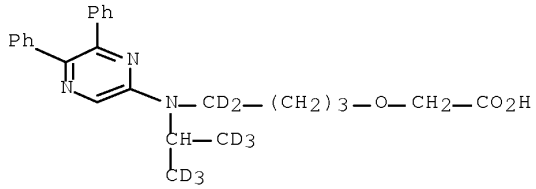


RN 1265295-48-4 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-

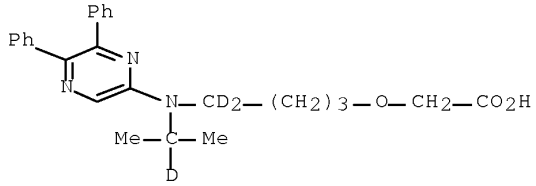
d4]amino]butoxy-4,4-d2]- (CA INDEX NAME)



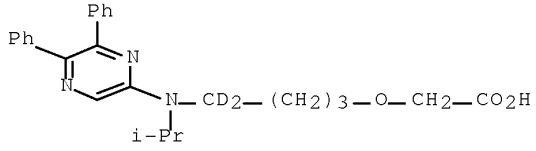
RN 1265295-49-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-4,4-d2]- (CA INDEX NAME)



RN 1265295-50-8 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-4,4-d2]- (CA INDEX NAME)

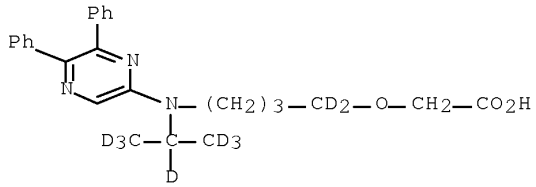


RN 1265295-51-9 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-4,4-d2]- (CA INDEX NAME)

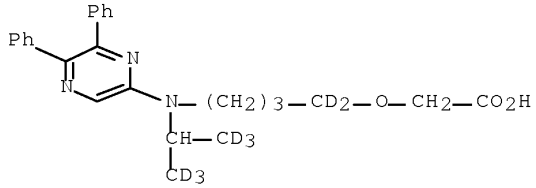


RN 1265295-52-0 HCAPLUS

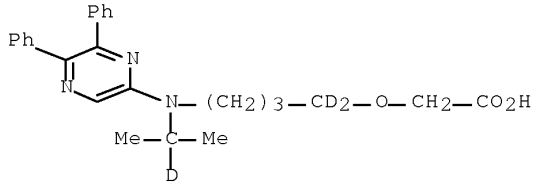
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1-d2]- (CA INDEX NAME)



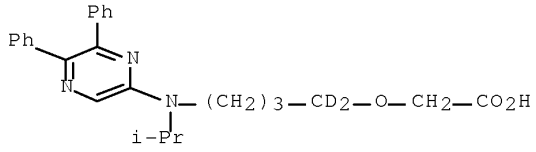
RN 1265295-53-1 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy-1,1-d2]- (CA INDEX NAME)



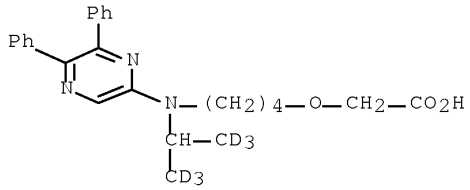
RN 1265295-54-2 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy-1,1-d2]- (CA INDEX NAME)



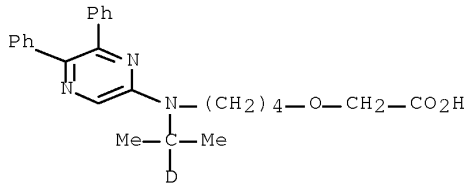
RN 1265295-55-3 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1-d2]- (CA INDEX NAME)



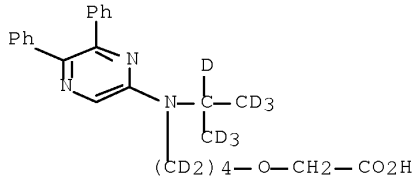
RN 1265295-56-4 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-2,2,2-d3]amino]butoxy]- (CA INDEX NAME)



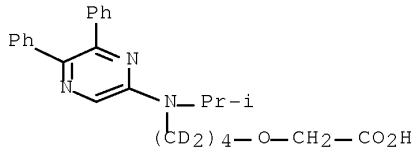
RN 1265295-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl-1-d)amino]butoxy]- (CA INDEX NAME)



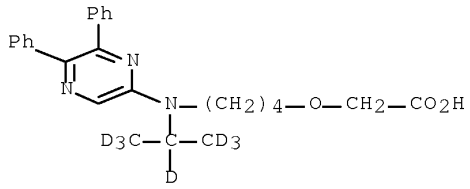
IT 1265295-10-0P 1265295-15-5P 1265295-20-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(diphenylpyrazine derivs. as PGI2 receptor agonists)
RN 1265295-10-0 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy-1,1,2,2,3,3,4,4-d8]- (CA INDEX NAME)



RN 1265295-15-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy-1,1,2,2,3,3,4,4-d8]- (CA INDEX NAME)

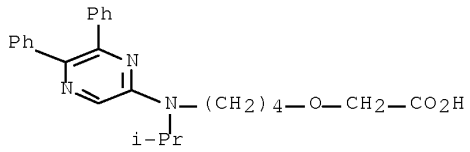


RN 1265295-20-2 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)[1-(methyl-d3)ethyl-1,2,2,2-d4]amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1251056 HCAPLUS Full-text
DOCUMENT NUMBER: 155:1448
TITLE: Selexipag: a selective prostacyclin receptor agonist that does not affect rat gastric function
AUTHOR(S): Morrison, Keith; Ernst, Roland; Hess, Patrick; Studer, Rolf; Clozel, Martine
CORPORATE SOURCE: Drug Discovery Department, Actelion Pharmaceuticals Ltd, Allschwil, Switz.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2010), 335(1), 249-255
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475085-57-5, ACT 333679
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selexipag and its metabolite ACT-333679 did not contract gastric fundus of rat)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:845010 HCAPLUS Full-text
DOCUMENT NUMBER: 153:164406
TITLE: Methods of identifying critically ill patients at increased risk of development of organ failure and compounds for the treatment hereof
INVENTOR(S): Johansson, Paer
PATENT ASSIGNEE(S): Thrombologic APS, Den.
SOURCE: PCT Int. Appl., 90pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2010075861	A2	20100708	WO 2009-DK50357		20091230
WO 2010075861	A3	20101007			
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA					
CA 2747310	A1	20100708	CA 2009-2747310		20091230
AU 2009335398	A1	20110721	AU 2009-335398		20091230
KR 2011115578	A	20111021	KR 2011-7017937		20091230
EP 2384196	A2	20111109	EP 2009-801149		20091230
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS					
CN 102271685	A	20111207	CN 2009-80153297		20091230
JP 2012514014	T	20120621	JP 2011-543978		20091230
ZA 2011004357	A	20120829	ZA 2011-4357		20091230
MX 2011006995	A	20110927	MX 2011-6995		20110628
US 20110268732	A1	20111103	US 2011-142935		20110630
PRIORITY APPLN. INFO.:			DK 2008-1844	A	20081230
			US 2009-161487P	P	20090319

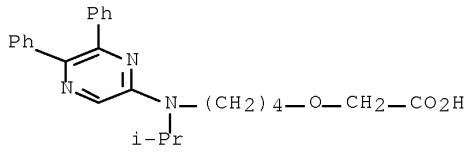
WO 2009-DK50357 W 20091230

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 475085-57-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods of identifying critically ill patients at increased risk of development of organ failure and compds. for treatment hereof)

RN 475085-57-5 HCAPLUS

CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

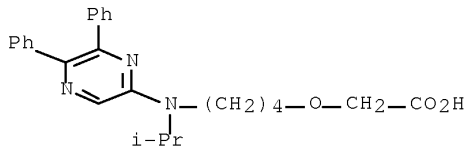
L9 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:214047 HCAPLUS Full-text
DOCUMENT NUMBER: 152:271363
TITLE: Therapeutic compositions containing macitentan and prostacyclin receptor agonists
INVENTOR(S): Clozel, Martine
PATENT ASSIGNEE(S): Actelion Pharmaceuticals Ltd, Switz.
SOURCE: PCT Int. Appl., 13pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010018549	A2	20100218	WO 2009-IB53553	20090812
WO 2010018549	A3	20100729		
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
AU 2009280843	A1	20100218	AU 2009-280843	20090812
CA 2731370	A1	20100218	CA 2009-2731370	20090812
AR 73031	A1	20101006	AR 2009-103113	20090812
KR 2011045006	A	20110503	KR 2011-7003547	20090812
EP 2315587	A2	20110504	EP 2009-786912	20090812

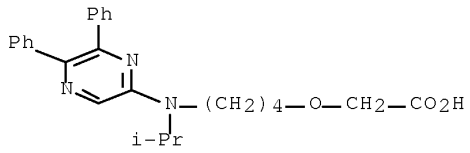
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS

CN 102099026	A	20110615	CN 2009-80127993		20090812
CN 102099026	B	20120829			
JP 2011530581	T	20111222	JP 2011-522608		20090812
MX 2011001625	A	20110329	MX 2011-1625		20110211
US 20110136818	A1	20110609	US 2011-58639		20110211
IN 2011CN01623	A	20111202	IN 2011-CN1623		20110308
ZA 2011001900	A	20120829	ZA 2011-1900		20110311
PRIORITY APPLN. INFO.:			WO 2008-IB53252	A	20080813
			WO 2009-IB53553	W	20090812

IT 475085-57-5, MRE 269 475085-57-5D, MRE 269, salts
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. containing macitentan and prostacyclin receptor agonists)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



L9 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:111452 HCAPLUS Full-text
DOCUMENT NUMBER: 152:184324
TITLE: Therapeutic agent for chronic renal failure
INVENTOR(S): Matsuda, Fuko; Iseki, Katsuhiko; Kurumatani, Hajimu; Miyamoto, Mitsuko
PATENT ASSIGNEE(S): Toray Industries, Inc., Japan
SOURCE: PCT Int. Appl., 39pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010010909	A1	20100128	WO 2009-JP63153	20090723
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2730599	A1	20100128	CA 2009-2730599	20090723
EP 2305653	A1	20110406	EP 2009-800423	20090723
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, AL, BA, RS				
KR 2011036572	A	20110407	KR 2011-7000559	20090723
CN 102105453	A	20110622	CN 2009-80128581	20090723
MX 2011000897	A	20110330	MX 2011-897	20110121
IN 2011KN00361	A	20111125	IN 2011-KN361	20110124
US 20110178103	A1	20110721	US 2011-55242	20110330
PRIORITY APPLN. INFO.:			JP 2008-190085 A	20080723
			WO 2009-JP63153 W	20090723

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

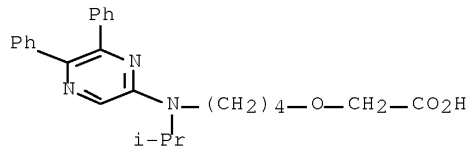
OTHER SOURCE(S): MARPAT 152:184324

IT 475085-57-5

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic agent for chronic renal failure)

RN 475085-57-5 HCAPLUS

CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1618864 HCAPLUS Full-text

DOCUMENT NUMBER: 152:67647

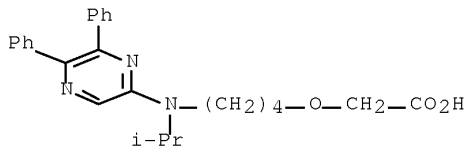
TITLE: Therapeutic agent for inflammatory bowel disease

INVENTOR(S): Kyoi, Takashi

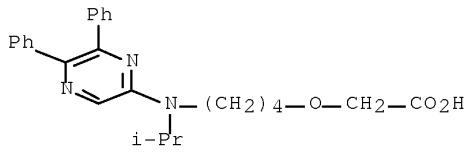
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 25pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157398	A1	20091230	WO 2009-JP61287	20090622
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2728161	A1	20091230	CA 2009-2728161	20090622
EP 2289518	A1	20110302	EP 2009-770108	20090622
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS				
KR 2011036537	A	20110407	KR 2010-7028238	20090622
CN 102065864	A	20110518	CN 2009-80124684	20090622
CN 102065864	B	20121121		
US 20110118254	A1	20110519	US 2010-791	20101222
PRIORITY APPLN. INFO.:			JP 2008-162640 A	20080623
			WO 2009-JP61287 W	20090622

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 152:67647
IT 475085-57-5 475085-57-5D, salt
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for inflammatory bowel disease)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



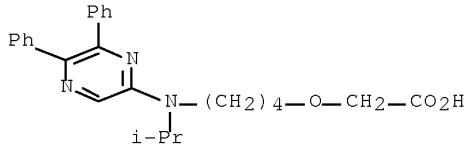
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1618854 HCAPLUS Full-text
DOCUMENT NUMBER: 152:67646
TITLE: Therapeutic agent for intestinal tract injury accompanying administration of a non-steroid anti-inflammatory agent
INVENTOR(S): Kyoi, Takashi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

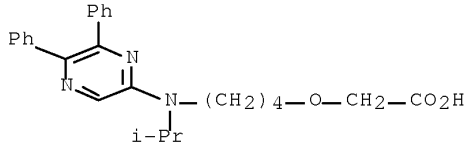
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157397	A1	20091230	WO 2009-JP61286	20090622

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-162639 A 20080623
OTHER SOURCE(S): MARPAT 152:67646
IT 475085-57-5 475085-57-5D, salt
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for intestinal tract injury accompanying administration of a non-steroid anti-inflammatory agents)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1618851 HCAPLUS Full-text
DOCUMENT NUMBER: 152:67707
TITLE: Therapeutic agent for spinal canal stenosis
INVENTOR(S): Kuwano, Keiichi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009157396	A1	20091230	WO 2009-JP61285	20090622
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2728089	A1	20091230	CA 2009-2728089	20090622
EP 2292231	A1	20110309	EP 2009-770106	20090622
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,				

IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS

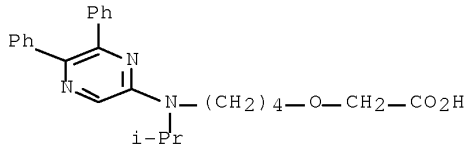
KR 2011033125	A	20110330	KR 2010-7027945		20090622
CN 102065863	A	20110518	CN 2009-80124683		20090622
US 20110105518	A1	20110505	US 2010-758		20101222
IN 2011CN00452	A	20111118	IN 2011-CN452		20110120
PRIORITY APPLN. INFO.:			JP 2008-162638	A	20080623
			WO 2009-JP61285	W	20090622

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

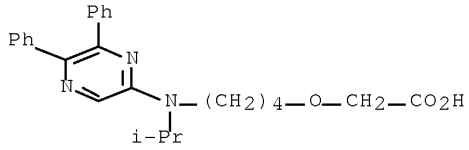
OTHER SOURCE(S): MARPAT 152:67707

IT 475085-57-5 475085-57-5D, deriv. and salts
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as therapeutic agents for spinal canal stenosis)

RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2009:1598176 HCAPLUS Full-text

DOCUMENT NUMBER: 152:67703

TITLE: Therapeutic agent for erectile dysfunction

INVENTOR(S): Higashioka, Masaya

PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan

SOURCE: PCT Int. Appl., 23pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

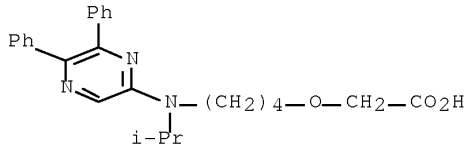
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009154246	A1	20091223	WO 2009-JP61071	20090618

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

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2008-160225 A 20080619
OTHER SOURCE(S): MARPAT 152:67703
IT 475085-57-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic agent for erectile dysfunction containing heterocyclic compds.)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2009:1080888 HCAPLUS Full-text
DOCUMENT NUMBER: 151:305248
TITLE: Fibrosis inhibitor
INVENTOR(S): Murakami, Koji; Toramoto, Takuya
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009107736	A1	20090903	WO 2009-JP53582	20090226

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

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

AU 2009218115	A1	20090903	AU 2009-218115		20090226
CA 2716554	A1	20090903	CA 2009-2716554		20090226
EP 2246336	A1	20101103	EP 2009-714302		20090226
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS					
KR 2010135726	A	20101227	KR 2010-7018956		20090226
CN 101959868	A	20110126	CN 2009-80106979		20090226
MX 2010008745	A	20100830	MX 2010-8745		20100809
US 20110015211	A1	20110120	US 2010-919885		20100827
IN 2010CN05979	A	20110422	IN 2010-CN5979		20100922
PRIORITY APPLN. INFO.:			JP 2008-46999	A	20080228
			WO 2009-JP53582	W	20090226

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 151:305248

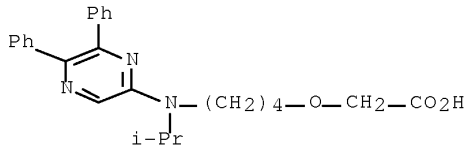
IT 475085-57-5 475085-57-5D, salts

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropylamino]butyloxy}acetate derivs. and salts as fibrosis inhibitors)

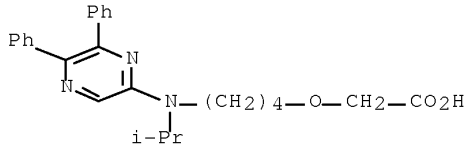
RN 475085-57-5 HCAPLUS

CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



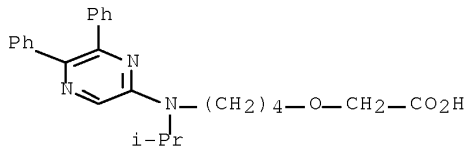
RN 475085-57-5 HCAPLUS

CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

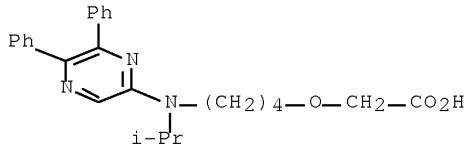
L9 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2008:1059866 HCAPLUS Full-text
DOCUMENT NUMBER: 149:299321
TITLE: A long-acting and highly selective prostacyclin receptor agonist prodrug, 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide (NS-304), ameliorates rat pulmonary hypertension with unique relaxant responses of its active form, {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}acetic acid (MRE-269), on rat pulmonary artery
AUTHOR(S): Kuwano, Keiichi; Hashino, Asami; Noda, Kumiko; Kosugi, Keiji; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., Kisshoin, Minami-Ku, Kyoto, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2008), 326(3), 691-699
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475085-57-5, MRE-269
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug NS-304 ameliorates pulmonary hypertension)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:1195229 HCAPLUS Full-text
DOCUMENT NUMBER: 148:39274
TITLE: Synthesis and evaluation of N-acylsulfonamide and N-acylsulfonylurea prodrugs of a prostacyclin receptor agonist

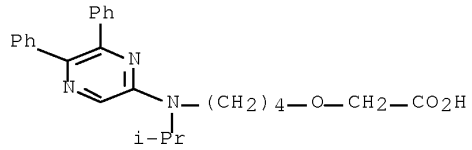
AUTHOR(S): Nakamura, Akio; Yamada, Tetsuhiro; Asaki, Tetsuo
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd, Kisshoin, Minami-Ku, Kyoto, 601 8550, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(24), 7720-7725
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:39274
IT 475085-57-5
RL: PKT (Pharmacokinetics); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(N-acylsulfonamide and N-acylsulfonylurea prodrugs of diphenylpyrazine prostacyclin receptor agonist)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

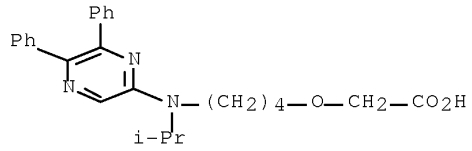
L9 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:1041397 HCAPLUS Full-text
DOCUMENT NUMBER: 147:514363
TITLE: Structure-activity studies on diphenylpyrazine derivatives: A novel class of prostacyclin receptor agonists
AUTHOR(S): Asaki, Tetsuo; Hamamoto, Taisuke; Sugiyama, Yukiteru; Kuwano, Keiichi; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., 14 Nishinosho-Monguchi-Cho, Kisshoin, Minami-ku, Kyoto, 601-8550, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(21), 6692-6704
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 147:514363
IT 475085-57-5P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(structure-activity studies on diphenylpyrazine derivs., a class of prostacyclin receptor agonists)
RN 475085-57-5 HCAPLUS

CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2007:976851 HCAPLUS Full-text
DOCUMENT NUMBER: 147:461873
TITLE: 2-{4-[5,6-(Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl) acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug
AUTHOR(S): Kuwano, Keiichi; Hashino, Asami; Asaki, Tetsuo; Hamamoto, Taisuke; Yamada, Tetsuhiro; Okubo, Kaori; Kuwabara, Kenji
CORPORATE SOURCE: Discovery Research Laboratories, Nippon Shinyaku Co., Ltd., Kyoto, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2007), 322(3), 1181-1188
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT 475085-57-5P, MRE 269
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(2-{4-[5,6-(Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl) acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS

RECORD (22 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

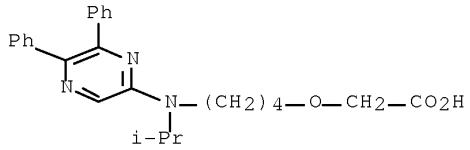
L9 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2002:849591 HCAPLUS Full-text
DOCUMENT NUMBER: 137:370112
TITLE: Preparation of derivatives of heterocyclic compounds such as pyridine, pyrimidine, 1,2,4-triazine, and pyrazine as antagonists of prostaglandin I2 receptor
INVENTOR(S): Asaki, Tetsuo; Hamamoto, Taisuke; Kuwano, Keiichi
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088084	A1	20021107	WO 2002-JP4118	20020425
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
TW 316055	B	20091021	TW 2002-108440	20020424
CA 2445344	A1	20021107	CA 2002-2445344	20020425
CA 2445344	C	20110726		
AU 2002253588	A1	20021111	AU 2002-253588	20020425
EP 1400518	A1	20040324	EP 2002-722772	20020425
EP 1400518	B1	20070117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002009249	A	20040608	BR 2002-9249	20020425
CN 1516690	A	20040728	CN 2002-808977	20020425
CN 1301973	C	20070228		
RU 2283835	C2	20060920	RU 2003-134190	20020425
PT 1400518	E	20070330	PT 2002-722772	20020425
ES 2276931	T3	20070701	ES 2002-722772	20020425
KR 921760	B1	20091015	KR 2003-7014044	20020425
JP 4479152	B2	20100609	JP 2002-585386	20020425
US 20040102436	A1	20040527	US 2003-476196	20031023
US 7205302	B2	20070417		
MX 2003009800	A	20040129	MX 2003-9800	20031024

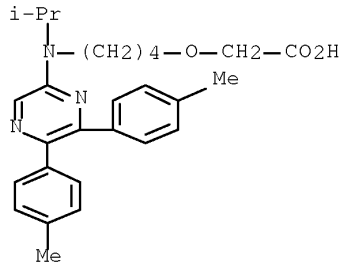
PRIORITY APPLN. INFO.: JP 2001-129765 A 20010426
WO 2002-JP4118 W 20020425

OTHER SOURCE(S): MARPAT 137:370112
IT 475085-57-5P 475085-60-0P 475085-62-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of derivs. of heterocyclic compds. as antagonists of prostaglandin I2 receptor platelet aggregation inhibitor, or remedy for chronic artery obstruction, intermittent limping, or peripheral artery

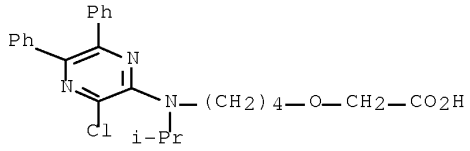
embolism)
RN 475085-57-5 HCAPLUS
CN Acetic acid, 2-[4-[(5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-60-0 HCAPLUS
CN Acetic acid, 2-[4-[[5,6-bis(4-methylphenyl)-2-pyrazinyl](1-methylethyl)amino]butoxy]- (CA INDEX NAME)



RN 475085-62-2 HCAPLUS
CN Acetic acid, 2-[4-[(3-chloro-5,6-diphenyl-2-pyrazinyl)(1-methylethyl)amino]butoxy]- (CA INDEX NAME)



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

---Logging off of STN---

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine Clozel
	Art Unit:	1627
	Examiner Name:	CARTER, Kendra, D.
Sheet 1 of 1	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
/K.C./		EP 0743307	11/20/1996	Tanabe Seiyaku Co., Ltd.	
/K.C./		EP 0658548	12/15/1994	Tanabe Seiyaku Co., Ltd.	

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
/K.C./		**IGLARZ, M., et al.,** "Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist", *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 327, No. 3, pp. 736-745, (2008).	

EXAMINER	/Kendra Carter/	DATE CONSIDERED	06/10/2013

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	**Art Unit**
	KENDRA D CARTER	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/26/2012	06/10/2013							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							

UNITED THERAPEUTICS CORP., EX1006, page 308
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	Art Unit
	KENDRA D CARTER	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (eDAN,PALM)	12/6/12	KDC
STN	12/6/12	KDC
Google (macitentan, PDE5 inhibitor, hypertension, tadalafil, sildenafil)	12/6/12	KDC
Search updated and reviewed	6/4/13	KDC

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC

CONFIRMATION NO. 5499

50446
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

PUBLICATION NOTICE

OC000000063259294

Title:THERAPEUTIC COMPOSITIONS

Publication No.US-2013-0210830-A9
Publication Date:08/15/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED THERAPEUTICS CORP., EX1006, page 310
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the final Office Action mailed June 20, 2013, the shortened statutory period for response ending September 20, 2013, Applicant provides the following remarks.

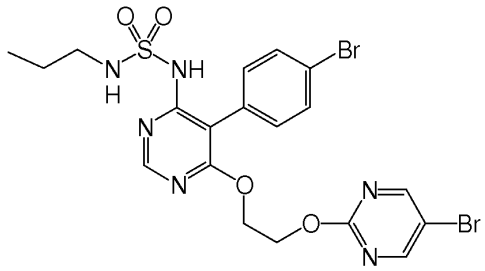
Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Listing of the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Previously Presented) 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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. (Previously Presented) The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound

UNITED THERAPEUTICS CORP., EX1006, page 312
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

6. (Previously Presented) The method according to claim 5, wherein said administration will not exceed one day.

7. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

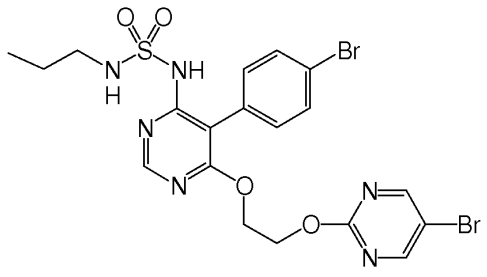
8. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

9. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. (Currently amended) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

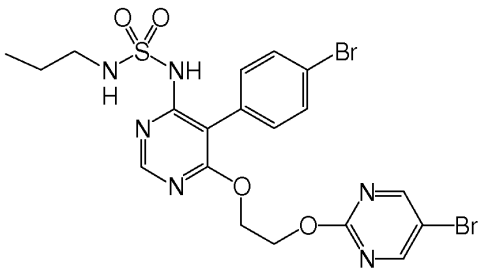


(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 313
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

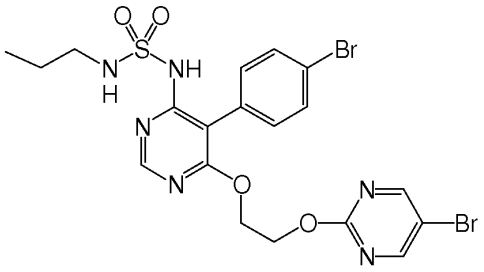
13. (Currently amended) A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. (Currently amended) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 314
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Remarks

Claims 1-14 are pending in this application. Claims 1-14 stand rejected. Claims 12-14 have been amended for clarification purposes. No new matter has been entered.

Rejection under 35 U.S.C. § 103(a)

Claims 1-14 stand rejected under 35 U.S.C. § 103 for alleged obviousness over International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") in view of International Publication No. WO 2006/026395 to Keyser et al. ("Keyser").

The Examiner asserts that Bolli teaches the instant compound of Formula I disclosed in Applicant's claims as an ET antagonist 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, portal hypertension, pulmonary hypertension and erectile dysfunction. *Office Action*, 1/17/2013, pp. 12-13. The Examiner further asserts that Keyser teaches that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension, and that pulmonary hypertension "relates to pulmonary arterial hypertension" (citing Keyser at paragraph 43). *Id.* The Examiner then concludes that it would have been "obvious and motivated" to select the instant compound of Formula I from Bolli to be combined with a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary arterial hypertension, because the compound of Formula I is an ET antagonist, and Keyser teaches that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension. *Id.*

Applicants argued that Keyser teaches away from the use of a compound such as the currently claimed compound of Formula I to be combined with a PDE5 inhibitor because the compound of formula I, like Bosentan, which is explicitly excluded from Keyser, is a dual ET_A:ET_B antagonist and therefore is not an optimum choice for Keyser's purpose. In response, the Examiner distinguished the compound of Formula I of the current invention from Bosentan, arguing that Bosentan is considered nonselective because it has an ET_A:ET_B selectivity ratio of 20, but the ethyl analog of the Applicants' claimed compound described in Bolli as Example 104 has an ET_A:ET_B selectivity ratio of 682.95, which is much more selective for ETA than ET_B than Bosentan. *Final Office Action*, 6/20/2013, pp. 15-16. Because the ethyl analog Example 104 is

UNITED THERAPEUTICS CORP., EX1006, page 315
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

more selective than Bosentan, the Examiner argued that it would be obvious for one skilled in the art to select the claimed compound of Formula I from Bolli, which is expected to have similar activity as Example 104, to be combined with Keyser to arrive at current claimed invention.

Applicant respectfully disagrees that the present invention is obvious over Bolli in combination with Keyser and respectfully request reconsideration once more. As previously argued, there is no legally sufficient motivation to select the compound of Applicants' claims from Bolli to be used with a PDE5 inhibitor because no ET_A:ET_B selectivity ratio is disclosed for that compound and there are other suitable candidates where the ET_A:ET_B selectivity ratios are disclosed in Bolli. The Examiner argued that one skilled in the art would be motivated to choose all of the compounds of Bolli that have greater selectivity for ET_A over ET_B with reasonable expectation of success. If all compounds disclosed in a reference are all suitable to be combined with another reference, however, there would be no need for the Federal Circuit to require the "lead compound" analysis. Second, as the Examiner admits, one skilled in the art would choose compounds "that have greater selectivity for ET_A over ET_B", not choose the compound that have the desired selectivity and then move on to analogs that has no disclosed activity.

In looking at Bolli, it may be true that one skilled in the art may start with the compounds disclosed in Table 1 where IC_{50} activities against ET_A and ET_B are shown. However, this still does not provide any reason to select Example 104 as the lead compound. In reading Keyser, which ***explicitly*** teaches the use of *ET_A-**selective** antagonists* in its combination therapy, Example 104 would not be an optimum choice as it has ET_B antagonistic activity. Although Keyser named only Bosentan as being an example of non-selective ET antagonist, the teaching nevertheless remains that ET_B antagonist "interferes with multiple pathways whereas use of a specific ET_A antagonist will act in a complimentary fashion for the multiple pathways". Keyser, p. 19, Paragraph [067]. Keyser explicitly explained the opposite effect of ET_A and ET_B:

> . . . ET_A causes vasoconstriction, while ET_B causes vasodilation . . . 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 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**

UNITED THERAPEUTICS CORP., EX1006, page 316
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

Id. pp. 19-20 at Paragraph [068]. Thus, the use of an ET_A-selective antagonist (with little or no antagonistic activity on ET_B) is a fundamental aspect of the Keyser teaching. In reading this in combination with Bolli, one skilled in the art would not be motivated to select a compound having ET_B activity as the lead compound. As such, one skilled in the art would not be motivated to choose the compound of Example 104 as the lead compound as there are other more suitable candidates disclosed in Boli. Applicant again respectfully points out that there are a number of compounds disclosed in Bolli that would be superior candidates in accordance with the Keyser teachings. See for example, the compounds of Examples 12, 24, 26, 34, 109, 110, 115, 117, 118, 145, 193 and 212. Given the numerous compounds in Bolli suitable for use in Keyser, there is no motivation to select compound 104 of Bolli as the lead compound.

Even if one skilled in the art were to choose Example 104 or any of Examples 12, 24, 26, 34, 109, 110, 115, 117, 118, 145, 193 and 212 to use in combination with Keyser, there is no motivation to then move on to the analogs disclosed on pages 24-28 of Bolli where no ET_A/ET_B activities are disclosed and choose a particular compound disclosed on page 28 as the compound of choice. The Examiner argued that one skilled in the art would expect the activity ratio to be similar to the N-ethyl analog of Example 104, which ET_A:ET_B selectivity ratio is disclosed in the specification. Applicants note that there are 16 other compounds disclosed on pages 24-28, which are structural similar to Example 104. In particular, the last three compounds on the right column of page 26; the 5^{th} compound on the left column and the 3^{rd} and 5^{th} compound on the right column on page 27; the last four compounds on the left column and the second, third, fifth and sixth compound on the right column of page 28 of Bolli are all structurally similar to Example 104. Nothing points to the compound on page 28 as the preferred compound.

In another scenario, according to the Examiner, one could also very well choose as a lead compound, Example 24 of Bolli which has comparable or even better selectivity against ET_A than Example 104. In that instant, the skilled artisan would then also have to consider the first six compounds on page 26 and the first four compounds on page 27 as possibilities as, according to the Examiner's logic, they are expected to have similar activities to Example 24. With so many

UNITED THERAPEUTICS CORP., EX1006, page 317
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

possibilities and no particular guidance, there is again no reason to select the first compound on the right column on page 28 of Bolli as the compound of choice.

Here, the claimed compound of formula (I), also known as Macitentan, is a dual ET_A/ET_B antagonist as confirmed in a later published article by Iglarz et al., Journal of Pharmacology and Experimental Therapeutics, Vol. 329, No. 3 (2008) ("Iglarz"), previously submitted in an Information Disclosure Statement. The author states:

> In Vivo Pharmacology Studies. Macitentan is best studied in vivo because this allows the study of the overall pharmacological effects of macitentan together with its metabolite. When administered to normotensive rats, **macitentan, like bosentan, increased plasma ET-1 concentration, confirming its dual blockade on both ET_A and ET_B receptors**. This increase occurred at a 10-fold lower dose than with bosentan, indicating a more potent pharmacological activity in vivo (Fig. 2). (emphasis added)

Thus, Macitentan (or the compound of formula (I) of the current invention), like Bosentan, is a dual ET_A-ET_B receptor antagonist[1]. Given the explicit disclosure in Keyser of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A-ET_B receptor antagonists such as Bosentan, it can be seen that Keyser teaches away from the use of Macitentan in its combination therapy with PDE5 inhibitors. Accordingly, Applicant respectfully asserts that the Examiner can only select Example 104 as the lead compound using hindsight of the current invention. The Examiner has not established a legally sufficient motivation to select the currently claimed compound to be used in combination with the teaching of Keyser. In the absence of such legally sufficient motivation, the present rejection cannot be maintained, and should be withdrawn for this reason alone.

The present invention is also not obvious because it produces an unexpected effect. As described in the instant specification, Applicants have surprisingly found that the combination of the compound of formula (I) with a compound having PDE5-inhibitory properties results in an

[1] In a recent study, Maguire et al., *Life Sciences* (2012) 91:681-686 found that "[f]or an antagonist to retain ET_A-selectivity *in vivo* it may be necessary to identify those compounds that have at least 1000 fold ET_A:ET_B selectivity in *in vitro* assays.". *Id.* at Abstract. According to this, to be ET_A selective *in vivo*, the *in vitro* selectivity ratio of ET_A:ET_B has to be at least 1000. Consequently, Macitentan would not qualify as an ET_A selective antagonist as it would not be considered to be ET_A selective *in vivo*.

UNITED THERAPEUTICS CORP., EX1006, page 318
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

unexpected effect in the treatment of diseases wherein vasoconstriction is involved. The results, shown in the specification, are summarized in the Table below:

Example	Model	PDE5 Inhibitor	ABC for PDE5 Inhibitor	ABC for Macitentan	ABC for PDE5 Inhibitor + Macitentan
1	Dahl salt-sensitive rat Model	Tadalafil	310	256	923
2	Spontaneously 25 hypertensive rat model	Tadalafil	286	44	444
3	Spontaneously 25 hypertensive rat model	Sildenafil	229	38	317

It can be seen that in all three Examples, the combination of the PDE5 inhibitor and the compound of Formula I (Macitentan) provided ABC values that were unexpected; i.e., greater than the sum of the ABC values for administration of either component alone. The Examiner argued that there is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog taught by Bolli. Applicants note that neither Bolli nor Keyser discloses any unexpected results of the N-ethyl analog in combination with a PDE5 inhibitor. Keyser simply teaches the use of an ET_A-selective antagonist in combination with a PDE5 inhibitor for the treatment of cardiac disorders such as PAH. Example 1 of Keyser simply shows that sildenafil (or Viagra) does not appear to impact sitaxsentan (or THELIN) pharmacokinetics while no data is shown for the efficacy study in Example 2. Therefore, Keyser does not show any unexpected result at all. In fact, according to Keyser, a compound such as the one claimed in the invention which has ET_B antagonistic activity is expected to interfere with vasodilation by interfering with the ability for ET_B to stimulate the production of nitrous oxide and prostacyclin, thereby interfering with the ability of nitrous oxide to activate guanyl cyclase and preventing the increase in cGMP level responsible for relaxing the blood vessel. Therefore, the fact that no reduced efficacy is observed in administering the claimed combination compared to PDE5 inhibitor alone or the compound of formula I alone is already unexpected, let alone seeing enhanced efficacy. Applicants further note that Macitentan (the compound of formula I claimed in the current invention) has been shown to increase in vivo preclinical efficacy compared to existing endothelin receptor antagonist

UNITED THERAPEUTICS CORP., EX1006, page 319
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

resulting from sustained receptor binding and tissue penetration properties. These properties (particularly the tissue penetration property) certainly cannot be predicted or known based on the disclosure of Bolli. Applicants respectfully submit that the claimed invention possesses unexpected results and therefore is unobvious.

In view of the preceding remarks, Applicant respectfully asserts that the present invention is not obvious in view of the combination of Bolli and Keyser, and respectfully requests withdrawal of this rejection.

Double Patenting Rejections

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). As best understood, the Office Action appears to base its rejection on the same rationale as the instant rejection under U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser. However, as discussed in detail above, there is no motivation to combine the compound claimed in the '781 patent with a PDE5 inhibitor as Keyser teaches away from this. Also, the instant invention possesses unexpected results as no reduced efficacy, but rather enhanced efficacy is observed in the combination, which is contrary to what one would expect from reading Keyser. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection for precisely the same reasons as set forth above in Applicant's response to the present rejection under U.S.C. § 103.

Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142, now U.S. Pat. No. 8,367,685 ("the '142 application") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). Applicant notes that the '142 application has now issued as U.S. Patent No. 8,367,685. The Office Action states that the '142 application (now the '685 patent) teaches the compound of Formula I to treat pulmonary arterial hypertension, and admits that the '685 patent does not teach "the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary hypertension, nor the administration schedule of claims 2-6 and 12-14." *Office Action* at page 6. The Office Action then asserts that it would be obvious to combine the

UNITED THERAPEUTICS CORP., EX1006, page 320
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary 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 combined to treat pulmonary hypertension." *Office Action* at page 7. Thus, the Office Action again appears to base its rejection on the same rationale as the instant rejection under U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser. However, as discussed in detail above, there is no motivation to combine the compound claimed in the '142 application (now the '685 patent) with a PDE5 inhibitor as Keyser teaches away from this. Even if a skilled artisan were to follow the Examiner's line of reasoning and assume that the antagonistic activity is similar to Example 104 of Bolli (which Applicants continue to disagree there is any motivation to do), one would expect the compound of the '142 Application to be a dual ET_A:ET_B. As such, it would not be obvious to combine this compound with a PDE5 inhibitor as Keyser teaches that ET_B antagonist would interfere with the efficacy. Contrary to Keyser's teaching, however, the combination claimed possesses unexpected results as there is no reduced efficacy, but in fact enhanced efficacy seen in administering the claimed combination. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection for precisely the same reasons as set forth above in Applicant's response to the present rejection under U.S.C. § 103.

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of U.S. Patent No. 8,268,847 ("the '847 patent") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). The present application is a continuation of the application leading to the '847 patent. Applicant will consider providing further argument or filing a terminal disclaimer over the '847 patent upon an indication of otherwise allowable subject matter in the present application.

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional fees, or credit any overpayment, to Deposit Account No. 50-4255.

UNITED THERAPEUTICS CORP., EX1006, page 321
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Respectfully submitted,

Date August 20, 2013

/Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 301
Millburn, NJ 07041
973-912-5232 phone
973-912-5236 fax

UNITED THERAPEUTICS CORP., EX1006, page 322
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Brittany La/Melanie Vasquez
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	16639463
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La/Melanie Vasquez
Filer Authorized By:	Brittany La
Attorney Docket Number:	AC-66-USC
Receipt Date:	20-AUG-2013
Filing Date:	05-SEP-2012
Time Stamp:	18:40:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	5841
Deposit Account	504255
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Maguire_et_al_Defining_the_Affinity_Receptor.pdf	4455978 8f4c983c186a2530a86b3b4d32d5232ab1501442	no	6
Warnings:					
Information:					
2		AC-66-USC_SIDS_08202013.pdf	159955 d4abe8ed0d13d75856949d77d261f89861c69e39	yes	4

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Transmittal Letter	1	2
Information Disclosure Statement (IDS) Form (SB08)	3	4

Warnings:					
Information:					
3		AC-66-USC_response_to_OA_mailed_June_20_2013.pdf	82301 c27301aa3a5145dc7bc6c7ceeef084d28c881363	yes	12

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response After Final Action	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	12

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30378 bd2f14a7f69364b4a3f2a4e195da2fcbfb3b97d8	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	4728612	

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.

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.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	CLOZEL ET AL.	)	Examiner:	Carter, Kendra D.
		)		
Serial No.:	13/604,148	)	Group Art Unit:	1627
		)		
Filed:	09/05/2012	)	Conf. No.:	5499
		)		
Title:	THERAPEUTIC COMPOSITIONS	)	Docket No.:	AC-66-USC

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicant respectfully requests that this Information Disclosure Statement be entered and the documents listed on the attached form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

The filing of this Information Disclosure Statement is not be be construed as a representation that a search has been made, nor construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability or prior art.

Pursuant to 37 C.F.R. §1.98(a), copies of references which are non US patents and patent applications are enclosed herein.

INFORMATION DISCLOSURE STATEMENT

Attached is the required fee in the amount of $180.00 in order to have this Information Disclosure Statement considered.

It is believed that no other fees are due and no other fees are required. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), the Commissioner is authorized to charge any additional fees, if needed, or credit any overpayment, to deposit account No. 50-4255. If there are any questions, especially ones relating to payments, please contact the undersigned, or if the undersigned is not available, please contact a representative of the firm. Please do not leave voicemails at the undersigned's phone number.

Respectfully submitted,

Date: August 20, 2013

By: S:/Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, New Jersey 07041
973-912-5232
973-912-5236 (fax)

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/604,148
Filing Date	September 5, 2012
First Named Inventor	CLOZEL
Art Unit	1627
Examiner Name	Carter, Kendra D.
Attorney Docket Number	AC-66-USC

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code	Publication date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		2011/0136818	06/09/2011	Clozel et al.	
		2013/0190336	07/25/2013	Adesuyi et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Country Code "Number "Kind Code (if known)Number-Kind Code	Publication date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant. 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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 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 Office, 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.**

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/604,148
Filing Date	September 5, 2012
First Named Inventor	CLOZEL
Art Unit	1627
Examiner Name	Carter, Kendra D.
Attorney Docket Number	AC-66-USC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), 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.
		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

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 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 Office, 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.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/604,148	Filing Date 09/05/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/20/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						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.

LIE
/Tina J. Barden/

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.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

RESPONSE UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the final Office Action mailed June 20, 2013, the shortened statutory period for response ending September 20, 2013, Applicant provides the following remarks.

Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Please enter.

/KDC/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 09/18/2013

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/18/2013	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com

UNITED THERAPEUTICS CORP., EX1006, page 334
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Continuation:

The present application is being examined under the pre-AIA first to invent provisions.

For purposes of appeal, the proposed amendments will be entered, but do not place the application in condition for allowance because of the reasons below. Thus, all rejection of claims 31-35, 40-44, 67-69, 74-49 and 84 are upheld.

> The Applicant argues that Keyser teaches away from the use of a compound such as the currently claimed compound of formula I. As previously argued, there is no legally sufficient motivation to select the compound of Applicants' claims from Bolli to be used with a PDE5 inhibitor because no ET_A:ET_B selectivity ratio is disclosed for that compound and there are other suitable candidates where the ET_A:ET_B selectivity ratios are disclosed in Bolli. In looking at Bolli, it may be true that one skilled in the art may start with the compounds disclosed in Table 1 where IC_{50} activities against ET_A and ET_B are shown. However, this still does not provide any reason to select Example 104. Keyser explicitly explained the opposite effect of ET_A and ET_B. Thus, the use of an ET_A-selective antagonist is a fundamental aspect of the Keyser teaching. Applicant again respectfully points out that there are a number of compounds disclosed in Bolli that would be superior candidates in accordance with the Keyser teachings. Even if one skilled in the art were to choose Example 104 or any of the other Examples to use in the combination with Keyser, there is no motivation to then move on to the analogs where not ET_A:ET_B activities are disclosed. Applicants note that there are 16 other compounds disclosed on pages 24-28, which are structurally similar to Example 104. In another scenario, one could also very well choose as a lead compound, Example 24 of Bolli which has comparable or even better selectivity against ET_A than Example 104. Thus, Macitentan (or the compound of formula (I) or the current invention), like Bosentan is a dual ET_A-ET_B receptor antagonist. Given the explicit disclosure in Keyser of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A:ET_B selectivity receptor antagonists such as Bosentan. The present invention also produces unexpected results. Macitentan and a PDE5 inhibitor provide more than additive effects of either compound alone. Applicants note that neither

> Bolli nor Keyser discloses any unexpected results of the N-ethyl analog in combination with a PDE5 inhibitor. Applicants further note that Macitentan has been shown to increase *in vivo* preclinical efficacy compared to existing endothelin receptor antagonist resulting from sustained receptor binding and tissue penetration properties, which cannot be predicted or known based on the disclosure of Bolli. The Applicant argues the above arguments apply to all double patenting rejections.

The Examiner disagrees for the same reasons given the previous response. The Examiner disagrees because Keyser et al. defines selective compounds for ET_A antagonist should display a relative receptor binding ratio of at least 100 (see paragraph 59). Keyser et al. also teaches that bosentan is considered nonselective because it has an ET_A:ET_B selectivity ratio of 20 (see paragraph 60). According to Bolli et al. the ethyl analog of the Applicants claimed compound has a ET_A:ET_B selectivity ratio of 682.95 (see page 93, compound 104; and page 6). Thus, the compound is much more selective for ET_A than ET_B, far from being considered as nonselective compared to bosentan, and fits the definition of an ET_A antagonist by Keyser et al. Further, one skilled in the art would be motivated to choose all the compounds of Bolli et al. that have greater selectivity for ET_A over ET_B with reasonable expectation of success and motivation that the combination with a PDE5 inhibitor would provide treatment for conditions such as hypertension and pulmonary hypertension. Selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the Applicant's specific selection. See e.g., *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960). Although the specific claimed compound is taught by Bolli et al. but not tested for its ET_A:ET_B selectivity ratio one

would expect it to be similar to the N-ethyl analog compound 104. Compounds that are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by –CH2- groups are generally of sufficiently close structural similarity that there is presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457,195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d1082,197USPQ 601 (CCPA 1978). One skilled in the art may start with those compounds with the highest ET_A selectivity but that does not preclude trying all compounds similar and/or those that fall within the definition of Keyser et al. Again, the rejection is not an anticipation rejection but one of obviousness. With regard to the unexpected and synergistic results, one 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 to treat the same claimed disorder is taught. There is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog taught by Bolli et al. for instance. With regard to the *in vivo* preclinical efficacy and tissue penetration, the Examiner is not clear of where the data is for these results and their comparison to the closes prior art the demonstrates unexpected results. Therefore the Applicant's arguments are non-persuasive to overcome the 35 U.S.C. 103(a) and obviousness type double patenting rejections.

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 9:30 am - 6:00 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/
Primary Examiner, Art Unit 1627

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 13/604,148	**Applicant(s)** CLOZEL, MARTINE	
	Examiner KENDRA D. CARTER	**Art Unit** 1627	**AIA (First Inventor to File) Status** No

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

THE REPLY FILED 20 August 2013 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☐ will not be entered, or (b) ☒ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation.
13. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 8/20/13
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: .
    Claim(s) objected to: .
    Claim(s) rejected: 1-14.
    Claim(s) withdrawn from consideration: .

/KENDRA D CARTER/
Primary Examiner, Art Unit 1627

UNITED THERAPEUTICS CORP., EX1006, page 339
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/604,148
Filing Date	September 5, 2012
First Named Inventor	CLOZEL
Art Unit	1627
Examiner Name	Carter, Kendra D.
Attorney Docket Number	AC-66-USC

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	Document Number Number-Kind Code	Publication date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/K.C./		2011/0136818	06/09/2011	Clozel et al.	
/K.C./		2013/0190336	07/25/2013	Adesuyi et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Country Code "Number "Kind Code (if known)Number-Kind Code	Publication date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant. 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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 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 Office, 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.**

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/604,148
Filing Date	September 5, 2012
First Named Inventor	CLOZEL
Art Unit	1627
Examiner Name	Carter, Kendra D.
Attorney Docket Number	AC-66-USC

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), 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.
/K.C./		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

Examiner Signature	/Kendra Carter/	Date Considered	08/28/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant. 1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 2 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 Office, 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	)	Examiner:	CARTER, Kendra D.
		)		
Serial No.:	13/604,148	)	Group Art Unit:	1627
		)		
Filed:	September 5, 2012	)	Confirmation No.:	5499
		)		
Title:	THERAPEUTIC COMPOSITIONS	)	Docket: AC-66-USC	

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

Pending claims 1-14 stand rejected for obviousness and obviousness-type double patenting. Applicants respectfully request for a Pre-Appeal Brief Review and reversal of the rejection based on the clear error in failing to apply the lead-formulation and motivation to modify framework. Applicants also seek reversal for the clear error in failing to consider the unexpected results provided. In support of the request, Applicants hereby submit arguments along with the following:

Notice of Appeal — attached hereto;
PTO/SB/33 — attached hereto;
Exhibit A — Listing of the Claims – attached hereto;

Rejection under 35 U.S.C. § 103(a)

Independent claim 1 of the present application is directed to a method for treating hypertension, pulmonary hypertension or pulmonary arterial hypertension, comprising administering to a patient an effective amount of a compound of formula (I) and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form. Independent claims 12, 13 and 14 are directed to methods of treating the same disorders by a specific method of administration of the compound of formula (I) and sildenafil or tadalafil. The Examiner rejected claims 1-14 under 35 U.S.C. § 103 for being obvious over International Pub. No. WO 2002/053557 to Bolli et al., ("Bolli") in view of International Pub. No. WO 2006/026395 to Keyser et al. ("Keyser").

The Examiner noted that Bolli teaches the instant compound of formula (I) on page 28 of the reference. Although Bolli does not teach a combination of the compound of formula (I) with a PDE5 inhibitor, the Examiner argued that the combination is obvious because Keyser teaches that ET_A antagonists and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat hypertension, pulmonary hypertension and pulmonary arterial hypertension. Keyser discloses a number of ET_A antagonists in paragraphs [062], [063] and in Table 1. Keyser does not disclose the compound of formula (I) of the present claims. Applicants respectfully disagree.

There is no motivation to select the instant compound of Formula (I) from page 28 of Bolli to combine with PDE5 inhibitor of Keyser because said compound of formula (I) is not the lead compound and is not taught to be ET_A selective.

The Federal Circuit has specifically held that the framework for analysis as to the obviousness of chemical formulations involves a "lead-modification" analysis similar to that involving novel compounds. *Unigene Laboratories, Inc. et al. v. Apotex, Inc., et al.,* 655 F.3d 1352, 1361-1362 (Fed. Cir. 2011), applying the analytical framework of *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.,* 492 F.3d 1350, 1356 (Fed. Cir. 2007) and its progeny. First, a lead or reference formulation is identified from the art, and then a flexible teaching-suggestion-motivation (TSM) test is applied to determine whether there is reason or motivation to modify the lead formulation to make the claimed invention with a reasonable expectation of success. *Id. See also, Ex parte Subramanyam, et al.,* B.P.A.I. Decision January 15, 2010, Appeal No. 2009-012300 pp. 7-8; *Ex parte Subramanyam*, B.P.A.I. Decision March 29, 2010, Appeal No. 2010-002463. *Unigene* elaborates on the well-established principle that neither general disclosures nor mere identification in the prior art of each component of a composition can establish that the combination as a whole would have been obvious. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (emphasis added). As the Supreme Court held in *KSR*, "it will be necessary . . . to determine whether there was an apparent reason to combine [or modify] the known elements [in the prior art] in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR Int'l., Co. v. Teleflex, Inc*., 127 S. Ct. 1727, 1740 – 1741 (2007).

Here, the Examiner argued that it would have been obvious to select the second compound on page 28 of Bolli to combine with a PDE5 inhibitor as taught by Keyser. Even though no ET_A and ET_B data are disclosed for the compound on page 28 of Bolli, the Examiner argued that Keyser defines selective ET_A antagonist useful for their invention to display a relative receptor binding ratio of at least 100. As such, according to the Examiner, one skilled in the art would be motivated to choose any of the compounds of Bolli that have greater selectivity for ET_A over ET_B with reasonable expectation of success and motivation that the combination with PDE5 inhibitor would provide treatment for hypertension and pulmonary hypertension. The Examiner further argued that because the compound on page 28 is structurally similar to Example 104 of Bolli, which has an activity ratio of about 683, the compound on page 28 of Bolli is therefore expected to have similar activity and therefore, is encompassed by Keyser.

The Examiner is effectively arguing that because Keyser teaches a broad genus (here ET_A antagonist), all species that fall under that genus (here, all compounds that fall under Keyser's definition of ET_A) would be obvious. This argument, however, has been rejected by the Federal Circuit. *See In re Baird*, 16 F.3d 380, 382, (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). Therefore, identification of a genus does not render the species *prima facie* obvious. If the analysis were to start with Keyser, one skilled in the art would not select Example 104 as a lead compound out of the universe of ET_A compounds (which extends beyond the Bolli reference) because Keyser does not point to Bolli. It is further noted that sitaxsentan, which is disclosed in the lead formuation of Keyser, has a high specificity for ET_A, being 6,500-fold more selective as an antagonist for ET_A compared to ET_B (see Keyser, p. 15, ¶ [058]). Therefore, one skilled in the art would not select Example 104, which has a much lower selectivity ratio of about 683 to replace sitaxsentan. If the analysis were to start with Bolli, the "most preferred" compounds are identified on page 23. There is no motivation to select Example 104 as the lead compound.

Even if Example 104 were chosen as the lead, there is no motivation to modify the lead compound to arrive at the compound of formula (I) claimed herein.

Even if one skilled in the art were to choose Example 104 as the lead, which Applicants continue to contest, there is no motivation to then move on to the analogs disclosed on pages 24-28 of Bolli where

UNITED THERAPEUTICS CORP., EX1006, page 343
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

ET_A/ET_B activities are not disclosed, and choose, without any guidance, the second compound disclosed on page 28 as the compound of choice to replace sitaxsentan in Keyser. The Examiner argued that one skilled in the art would expect the activity ratio of the compound on page 28 to be similar to the N-ethyl analog of Example 104, which ET_A:ET_B selectivity ratio is disclosed in Bolli. Applicants respectfully disagree. Biological activities are generally unpredictable and cannot be extrapolated in the abstract as the Examiner did. Even if biological activities can be extrapolated, there are 16 other compounds disclosed on pages 24-28, which are structural similar to Example 104. Nothing specifically points to the second compound on page 28 as the preferred compound. Selecting the compound of Applicant's claims from Bolli would require choosing it from among the over 200 Bolli examples, without the benefit of any ET_A and ET_B inhibition data, despite the presence in Bolli of 134 compounds that did have ET_A-ET_B binding data. Clearly, such a selection could only be made using impermissible hindsight, with Applicant's disclosure as a guide.

Alternatively, one could also very well choose as a lead compound, Example 24 of Bolli which has comparable or even better selectivity against ET_A than Example 104. In that instant, the skilled artisan would then also have to consider the first six compounds on page 26 and the first four compounds on page 27 as possibilities as, according to the Examiner's logic, they are expected to have similar activities to Example 24. With so many possibilities and no particular guidance, there is again no reason to select the second compound on page 28 of Bolli as the compound of choice. With other possible lead compounds and an infinite number of modifications that could be made to these leads, there clearly is no finite number of predictable solutions to the problem here. The Federal Circuit in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs, Inc.* 520 F.3d 1358, 1365 (Fed. Cir. 2008) specifically rejected an analysis which starts off with "simply retrac[ing] the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention [ ] was obvious" as similarly done by the Examiner here in this case. The Federal Circuit specifically requires "a flexible TSM test[, which] remains the primary guarantor against a non-statutory hindsight analysis".

Keyser specifically teaches away from using a compound having non-selective ET activity, particularly compounds having ET_B antagonistic activity.

Keyser teaches that "use of 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". P. 19, ¶ [067]. Keyser explicitly excludes Bosentan because it works by blocking both ET_A and ET_B. P. 19-20, ¶ [068]. Keyser explains the opposite effect of ET_A and ET_B as follows:

> . . . ET_A causes vasoconstriction, while ET_B causes vasodilation . . . 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 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.

UNITED THERAPEUTICS CORP., EX1006, page 344
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Id. (emphasis added). Thus, the use of an ET_A-selective antagonist (with little or no antagonistic activity on ET_B) is a fundamental aspect of the Keyser teaching. In reading this in combination with Bolli, one skilled in the art would not be motivated to select a compound having ET_B activity as the lead compound as there would be no expectation of success. As such, one skilled in the art would not be motivated to choose the compound of Example 104, which as ET_B activity, as the lead compound. One skilled in the art also would not select the second compound on page 28 of Bolli to be combined with Keyser because if one presumes activity to be similar to Example 104, the combination would not be an ideal choice. Accordingly, Applicants respectfully assert that the Examiner can only select Example 104 as the lead compound and identify motivation to modify to the compound on page 28 of Bolli using hindsight of the current invention. The Examiner has not established a legally sufficient motivation to select the currently claimed compound to be used in combination with the teaching of Keyser. In the absence of such legally sufficient motivation, the present rejection cannot be maintained, and should be withdrawn.

The present invention is also not obvious because it produces an unexpected effect.

According to Keyser, a compound which has ET_B antagonistic activity is expected to interfere with vasodilation and therefore is expected to be less effective in combination with a PDE5 inhibitor (discussed above).

The claimed compound of formula (I), now known as Macitentan, has an *in vitro* ET_A:ET_B antagonistic activity of about 1:782 as can be calculated from the information provided in a later-published reference Iglarz et al., *Journal of Pharmacology and Experimental Therapeutics*, Vol. 329, No. 3 (2008) ("Iglarz"), previously submitted in an Information Disclosure Statement. This compound, however, is confirmed to exhibit dual ET_A/ET_B antagonistic activity. For instance, Iglarz shows in Table 4 on page 740 that in a functional assay, the selectivity of ET_A/ET_B is only 50:1. Significantly, in an *in vivo* study, the author states:

> **In Vivo Pharmacology Studies.** Macitentan is best studied in vivo because this allows the study of the overall pharmacological effects of macitentan together with its metabolite. When administered to normotensive rats, **macitentan, like bosentan, increased plasma ET-1 concentration, confirming its dual blockade on both ET_A and ET_B receptors**. This increase occurred at a 10-fold lower dose than with bosentan, indicating a more potent pharmacological activity in vivo (Fig. 2). (emphasis added)

Thus, Macitentan (or the compound of formula (I) of the current invention), like Bosentan, is considered by those skilled in the art to be a dual ET_A-ET_B receptor antagonist. As also confirmed by a later-published article by Bolli et al., *J. Med. Chem.* (2012) 55:7849-7861 (submitted herewith), Macitentan was selected not only because of the increased potency on the ET_A receptor, but because it also blocks the ET_B receptor in vivo. *Id.* at p. 7850 and 7855. Given the explicit disclosure in Keyser of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A-ET_B receptor antagonists such as Bosentan, one skilled in the art would not have any expectation of success in the use of Macitentan, a dual ET_A/ET_B antagonist, in combination with a PDE5 inhibitor.

Contrary to Keyser, Applicants have surprisingly found that the combination of the compound of formula (I), i.e., Macitentan, with a compound having PDE5-inhibitory properties results in an unexpected effect in the treatment of diseases wherein vasoconstriction is involved. The results, shown in the specification in Examples 1-3, are summarized in the Table below:

Example	Model	PDE5 Inhibitor	ABC for PDE5 Inhibitor	ABC for Macitentan	ABC for PDE5 Inhibitor +

UNITED THERAPEUTICS CORP., EX1006, page 345
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

					Macitentan
1	Dahl salt-sensitive rat Model	Tadalafil	310	256	923
2	Spontaneously 25 hypertensive rat model	Tadalafil	286	44	444
3	Spontaneously 25 hypertensive rat model	Sildenafil	229	38	317

It can be seen that in all three Examples, the combination of the PDE5 inhibitor and the compound of Formula I (or Macitentan) provided ABC values that were unexpected; i.e., greater than the sum of the ABC values for administration of either component alone.

The Examiner argued that there is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog taught by Bolli. Applicants note that neither Bolli nor Keyser discloses any unexpected results of the N-ethyl analog in combination with a PDE5 inhibitor. Keyser simply teaches the use of an ET_A-selective antagonist in combination with a PDE5 inhibitor for the treatment of cardiac disorders such as PAH. Example 1 of Keyser simply shows that sildenafil does not appear to impact sitaxsentan pharmacokinetics while no data is shown for the efficacy study in Example 2. Therefore, Keyser does not show any unexpected result at all.

The Examiner failed to consider the unexpected results provided in the application. In view of the preceding remarks, Applicant respectfully asserts that the present invention is not obvious in view of the combination of Bolli and Keyser, and respectfully requests withdrawal of this rejection.

Double Patenting Rejections

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") in view of International Pub. No. WO 2002/053557 to Bolli et al., ("Bolli") and International Pub. No. WO 2006/026395 to Keyser et al. ("Keyser"). Claims 1-14 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142 ("the '142 application") in view of International Pub. No. WO 2002/053557 to Bolli et al., ("Bolli") and International Pub. No. WO 2006/026395 to Keyser et al. ("Keyser"). Applicants note that the '142 application has now issued as U.S. Patent No. 8,367,685. The Office Action appears to base its rejection on the same rationale as the instant rejection under 35 U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser. However, as discussed in detail above, there is no motivation to combine the compound claimed in the '142 application (now the '685 patent) or the '781 patent with a PDE5 inhibitor as Keyser teaches away from this combination. Contrary to Keyser's teaching, the combination claimed possesses unexpected results as there is no reduced efficacy, but in fact enhanced efficacy seen in administering the claimed combination (discussed above). In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection under obviousness-type double patenting.

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of the parent case, U.S. Patent No. 8,268,847 ("the '847 patent") in view of International Publication No. WO 2002/053557 to Bolli et al., ("Bolli") and International Publication No. WO 2006/026395 to Keyser et al. ("Keyser"). The present application is a continuation of the application leading to the '847 patent. Applicant will consider providing further argument or filing a terminal disclaimer over the '847 patent upon an indication of otherwise allowable subject matter in the present application.

UNITED THERAPEUTICS CORP., EX1006, page 346
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Respectfully submitted,

Date October 21, 2013

/Brittany La/

Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
973-912-5232 phone
973-912-5236 fax

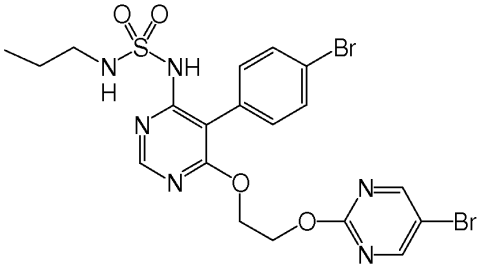
UNITED THERAPEUTICS CORP., EX1006, page 347
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Exhibit A

Listing of the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Previously Presented) 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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. (Previously Presented) The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

6. (Previously Presented) The method according to claim 5, wherein said administration will not exceed one day.

7. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

8. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

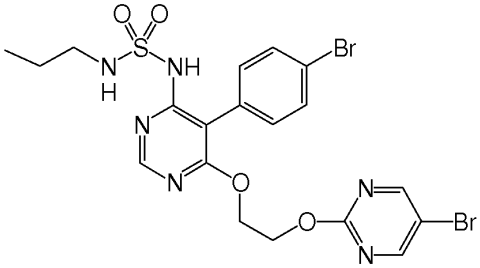
9. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

UNITED THERAPEUTICS CORP., EX1006, page 348
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

10. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

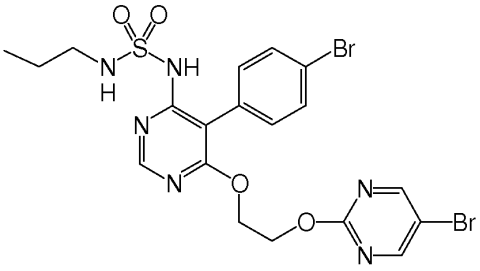
12. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

13. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

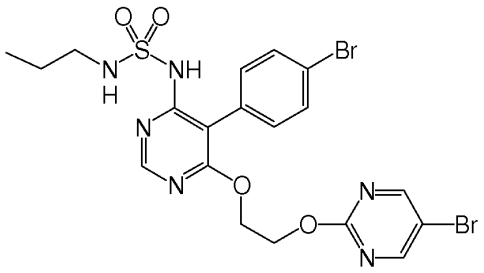


(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):

UNITED THERAPEUTICS CORP., EX1006, page 349
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 350
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Brittany La
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt	
EFS ID:	17186794
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La
Filer Authorized By:	
Attorney Docket Number:	AC-66-USC
Receipt Date:	22-OCT-2013
Filing Date:	05-SEP-2012
Time Stamp:	00:01:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1000
RAM confirmation Number	9016
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Notice of Appeal Filed	AC66USC_Notice_Appeal_10212013.pdf	98512 cfbdbd893b2b4c801cbd850f2fba029153785177	no	1
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	AC66USC_PreAppeal_Brief_10212013.pdf	110695 637343f65d758d8890b8514c8934dc20c11c21f7	no	1
Warnings:					
Information:					
3	Pre-Brief Conference request	AC-66-USC_Preappeal_Brief_Sept_20_2013_Final.pdf	83557 592c86614553c6b32cad56d53236d77a26986666	no	9
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	31759 8917b4eb08dc551157dda53aa34eeb5fc5cf6588	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	324523		

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.

PTO/SB/31 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Docket Number (Optional): AC-66-USC

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on FILED ELECTRONICALLY

Signature _____

Typed or printed name _____

In re Application of: Martine CLOZEL

Application Number	Filed
13/604,148	September 15, 2012

For: THERAPEUTIC COMPOSITIONS

Art Unit	Examiner
1627	Kendra D. CARTER

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 800.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☑ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-4255 .

☑ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

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.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☑ attorney or agent of record. Registration number 58,337.

☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

/Brittany La/
Signature

Brittany La
Typed or printed name

(973)912-5232
Telephone number

October 21, 2013
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.31. 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, 1.14 and 41.6. 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Doc Code: AP.PRE.REQ

PTO/SB/33 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): AC-66-USC

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on FILED ELECTRONICALLY

Signature

Typed or printed name

Application Number	Filed
13/604,148	September 15, 2012

First Named Inventor: THERAPEUTIC COMPOSITIONS

Art Unit	Examiner
1627	Kendra D. CARTER

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 58337.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/Brittany La/
Signature

Brittany La
Typed or printed name

973-912-5232
Telephone number

October 21, 2013
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. 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, 1.14 and 41.6. 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: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

Miscellaneous Communication

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

A pre-appeal brief along with Form PTO/SB/33 and the notice of appeal were submitted with a one-month extension of time. The reference Bolli et al., *J. Med. Chem.* (2012) 55:7849-7861 discussed in the pre-appeal brief was erroneously omitted from the Exhibit. Therefore, Applicants submit herewith said reference as Exhibit B. Applicants earnestly request consideration along with the pre-appeal brief. Submitted herewith is an extension of time fee in the amount of $400.00, the difference between the amount for a two-month extension of time and $200 previously submitted. Should this amount be incorrect, the Commissioner is authorized to charge any fees due during the pendency of this application (except for the payment of the issue fees), or credit any over payment to Deposit Account No. 50-4255.

Respectfully submitted,

Date October 22, 2013

/Brittany La/
Brittany La
Reg. No. 58,337

Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
973-912-5232 phone
973-912-5236 fax

EXHIBIT B

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

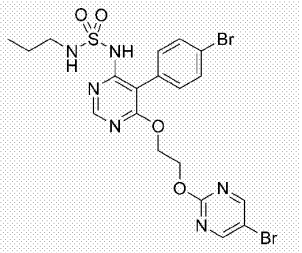
The Discovery of *N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N*′-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist

Martin H. Bolli,* Christoph Boss, Christoph Binkert, Stephan Buchmann, Daniel Bur, Patrick Hess, Marc Iglarz, Solange Meyer, Josiane Rein, Markus Rey, Alexander Treiber, Martine Clozel, Walter Fischli, and Thomas Weller

Drug Discovery Chemistry, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

Supporting Information

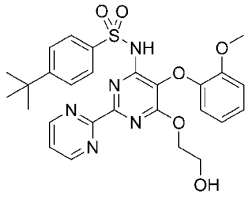
ABSTRACT: Starting from the structure of bosentan (**1**), we embarked on a medicinal chemistry program aiming at the identification of novel potent dual endothelin receptor antagonists with high oral efficacy. This led to the discovery of a novel series of alkyl sulfamide substituted pyrimidines. Among these, compound **17** (macitentan, ACT-064992) emerged as particularly interesting as it is a potent inhibitor of ET_A with significant affinity for the ET_B receptor and shows excellent pharmacokinetic properties and high in vivo efficacy in hypertensive Dahl salt-sensitive rats. Compound **17** successfully completed a long-term phase III clinical trial for pulmonary arterial hypertension.



INTRODUCTION

Over the past decade, our understanding of the function of endothelin (ET) has evolved from describing it as a purely vascular factor regulating blood pressure[1−4] to recognizing it as a hormone influencing many cellular processes such as proliferation, apoptosis, and migration leading to tissue hypertrophy, remodeling, fibrosis, and inflammation.[5−7] The three structurally closely related peptides, named endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3), are among the most potent vasoconstrictors known in humans. They convey their action through binding to two G-protein coupled receptors called ET_A and ET_B. Among the three isopeptides, ET-1 appears to be the key player in the cardiovascular system. ET-2 and ET-3 are specifically expressed in the gastrointestinal tract and the brain, respectively.[8,9] On the vascular side, ET_A receptors are mainly expressed on smooth muscle cells, mediating vasoconstriction, while ET_B receptors expressed on endothelial cells and smooth muscle cells cause vasodilation and vasoconstriction, respectively. In addition, a wealth of tissue cells such as cardiomyocytes, renal cortex, and medulla cells, fibroblasts, macrophages, and neurons produce ET-1 and/or express the two ET receptors, illustrating that the ET system is not confined to the vasculature only.[9−11] Cross talk and receptor heterodimer formation has been proposed for the two ET receptors.[6,12−15] Both ET_A and ET_B receptors are involved in mediating ET-1 deleterious effects in diseases such as chronic heart failure, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, or kidney disease.[6,7,10,16] Furthermore, in many pathological situations, the ET system is up-regulated and a change in the ET_A/ET_B expression ratio in favor of ET_B is observed in diseased tissue.[11,17−19] Several studies corroborate that increased activity of the ET system in tissue correlates with disease severity.[20,21]

A large number of synthetic endothelin receptor antagonists have been investigated preclinically, and several small molecule inhibitors have been studied in clinical trials for chronic heart failure, hypertension, cancer, and fibrosis.[5,22−27] Today, the dual ET_A/ET_B receptor antagonist bosentan (**1**, Figure 1)[28−30] and the ET_A selective antagonist (*S*)-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoic acid (ambrisentan)[31−33] are approved treatments for pulmonary arterial hypertension.



1 (Bosentan)
IC_{50} ET_A 45 nM
ET_B 202 nM

Figure 1. Structure and in vitro activity of compound **1**. IC_{50} values as measured with a ^{125}I-ET-1 binding assay.

Received: June 28, 2012
Published: August 3, 2012

ACS Publications © 2012 American Chemical Society

UNITED THERAPEUTICS CORP., EX1006, page 359
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

When we initiated our medicinal chemistry program to identify a follow-up compound to sulfonamide **1** (Figure 1), we decided that compound **1** should not only serve as the structural starting point for our quest for novel endothelin antagonists but should also represent the benchmark against which we gauge our novel compounds. A candidate suitable for clinical development needs to meet the following requirements: (1) The compound has to show a significantly increased potency on the ET_A receptor when compared to compound **1**. (2) The compound should block the ET_B receptor in vivo. (3) The compound needs to demonstrate oral efficacy superior to the one of compound **1** as assessed by measuring arterial blood pressure in conscious hypertensive Dahl salt-sensitive rats.[34−36] (4) Pharmacokinetic properties assessed in animals must support once daily dosing in humans. (5) The compound should easily distribute into tissue in order to also reach ET receptors expressed in the tissue. (6) Because compound **1** inhibits the canalicular bile salt export pump,[37] a candidate compound must be devoid of bile salt transport inhibition.

In the paragraphs below, we describe our efforts aimed at identifying a compound that meets all of the above criteria.

RESULTS AND DISCUSSION

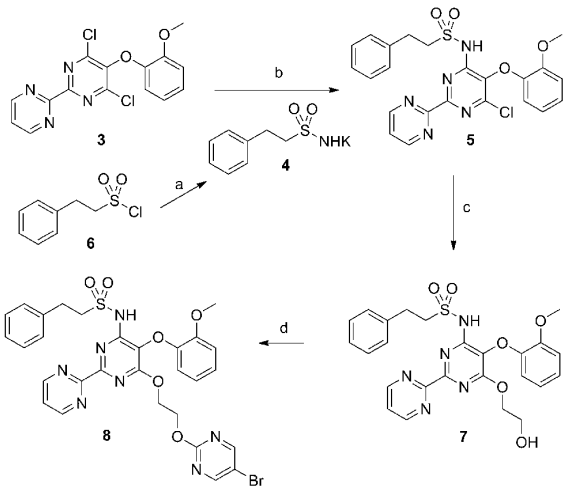
Synthesis. The following description of the synthesis of a prototypical sulfonamide (Scheme 1) and sulfamide (Scheme 2 and 3) endothelin receptor antagonist shall illustrate the general approach chosen to prepare the compounds discussed in this manuscript.

The preparation of the sulfonamide derivatives was carried out as previously described[38−42] and usually started by reacting a dichloro-pyrimidine building block[43,44] (e.g., **3**) with a sulfonamide potassium salt (e.g., **4**) in DMSO at room temperature to give the monochloro-pyrimidine intermediate (e.g., **5**). The sulfonamide potassium salts were readily accessible by treating the respective sulfonyl chloride (e.g., **6**) with ammonia, followed by potassium *tert*-butylate in methanol, while the necessary dichloro-pyrimidines were obtained as described in the literature.[40,42−46] The monochlorides such as **5** were treated with a freshly prepared solution of sodium in ethylene glycol at elevated temperatures to give the corresponding alcohols (e.g., **7**). The alcohols were dissolved in THF and deprotonated with 2.5 equiv of sodium hydride and reacted with the respective 2-chloro- or 2-(methylsulfonyl) pyrimidines at elevated temperature. As reported earlier,[47] these pyrimidines are either commercially available or prepared according to literature procedures.[48−52] Final products such as **8** were obtained in good yields as white to beige powders after crystallization from methanol.

The preparation of the various sulfamide building blocks needed for the synthesis of our sulfamide based endothelin receptor antagonists is exemplified with the propyl-sulfamide potassium salt **13** shown in Scheme 2.[40] The procedure starts by reacting chlorosulfonyl isocyanate (**9**) dissolved in dichloromethane at 0 °C with 1 equiv of *tert*-butanol to give the BOC-protected amino-sulfonyl-chloride (**10**), which was subsequently added slowly to a solution of 1 equiv of the respective amine (e.g., *n*-propylamine) in the presence of 3 equiv of triethylamine in dichloromethane at 0 °C. The mixture was stirred overnight to drive the reaction to completion and was then concentrated. The residue was dissolved in a large volume of ethyl acetate. To avoid extraction of the BOC-protected sulfamides such as **11** into water, reagents and salts were removed by washing the ethyl acetate solution very carefully with a small volume of water and brine only. The organic extract was dried, and the sulfamide **11** was isolated by evaporating the solvent. This material was dissolved in approximately 5 M HCl in dioxane to affect BOC-deprotection. After stirring the mixture at room temperature for 4−8 h, the solvent was evaporated to give sulfamide **12**. The potassium salt **13** was obtained by dissolving **12** in methanol followed by the addition of potassium *tert*-butylate and subsequent evaporation of the solvent. Purification of the potassium salt **13** was achieved by trituration in diethylether and drying under high vacuum. Overall yields of the above process were good to excellent.

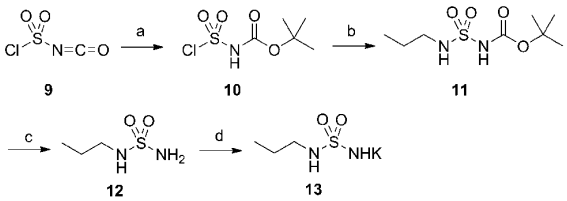
Synthesis of the sulfamide based endothelin receptor antagonists followed the preparation of the corresponding sulfonamide analogues. As an example, the preparation of sulfamide **17** is outlined in Scheme 3. Hence, reacting a dichloro-pyrimidine building block (e.g., **14**[42]) with a sulfamide

Scheme 1. General Synthesis of Sulfonamide Endothelin Receptor Antagonists Exemplified with 8[a]



[a]Reagents and conditions: (a) (i) **6**, NH_3 in MeOH, rt, 16 h, (ii) MeOH, KOtBu, rt 3 h, 83−89% over 2 steps; (b) **3**, DMSO, rt, then **4**, rt, 16 h, 89%; (c) ethylene glycol, Na, 2 h, then **5**, 70−90 °C, 18 h, 73−91%; (d) **7**, THF, NaH, 1 h, then 2-chloro-5-bromopyrimidine, 75 °C, 2 h, 43%.

Scheme 2. Synthesis of Sulfamide Potassium Salt Building Blocks[a]

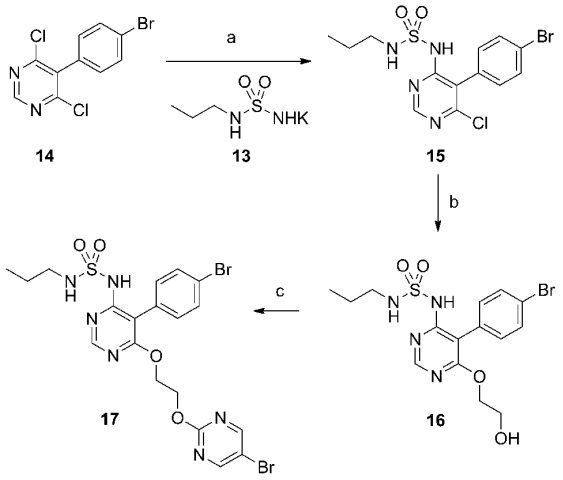


[a]Reagents and conditions: (a) *tert*-BuOH, DCM, 0 °C to rt, 1 h; (b) add mixture prepared in (a) to propylamine, NEt_3, DCM, 0 °C then 16 h rt; (c) 5 M HCl in dioxane, rt, 4−8 h; (d) MeOH, KOtBu, rt, 3 h, 46−98% over 4 steps.

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 360
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Scheme 3. General Synthesis of Sulfamide Endothelin Receptor Antagonists Exemplified with 17[a]



[a]Reagents and conditions: (a) **14**, DMSO, rt, **13**, rt, 24–72 h, 83–93% (b) ethylene glycol, DME, KOtBu, 10 min, then **15**, 100 °C, 18–24h, 86–89%; (c) **16**, THF, NaH, 0.5–1 h, then 2-chloro-5-bromopyrimidine, 60–75 °C, 2 h, 88%.

potassium salt such as **13** in DMSO at room temperature for 24–48 h gave the monochloro-pyrimidine intermediates (e.g., **15**). The ethylene-glycol side chain was introduced by applying similar conditions as described for the synthesis of the sulfonamides. Alternatively, the monochloride (e.g., **15**) was added to a mixture of 3 equiv of potassium *tert*-butylate and about 40 equiv of ethylene glycol in dimethoxyethane. These mixtures were usually heated to 90–100 °C for 24–70 h to furnish the corresponding alcohols (e.g., **16**) in yields of 70–90%. The final step, the attachment of the substituted pyrimidine, was performed as described for the sulfonamide derivatives in Scheme 1. For the preparation of compound **17**, 2-chloro-5-bromo-pyrimidine was used. In general, the target compounds could be purified easily by recrystallization from methanol.

In Vitro SAR Discussion. Inspired by the structure of Tanabe's clinical development compound *N*-(6-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-5-(*p*-tolyl)pyrimidin-4-yl)-4-(1-hydroxy-2-methylpropan-2-yl)benzenesulfonamide (T-0201, **2**)[53] (Figure 2), we were curious to learn how the introduction of a pyrimidine to the ethylene glycol moiety of compound **1** would

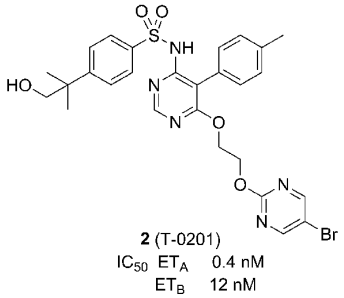
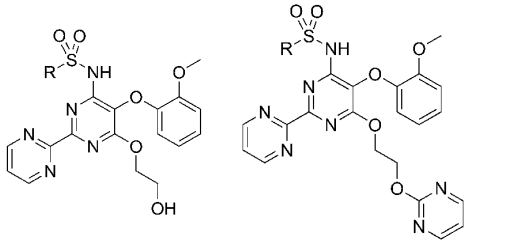


Figure 2. Structure and in vitro activity of compound **2**. IC_{50} values as measured with a ^{125}I-ET-1 binding assay.

influence its affinity for the two endothelin receptors. In a first study illustrated by the compounds listed in Table 1, we

Table 1. Effect of Additional Pyrimidine at Ethylene Glycol[a]



R	compd	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]	compd	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
4-*tert*-butyl phenyl	**1**	45.0	202	**18**	4.3	76
phenethyl	**19**	25.7	1131	**20**	8.0	465
methyl	**21**	4534	9506	**22**	739	1765

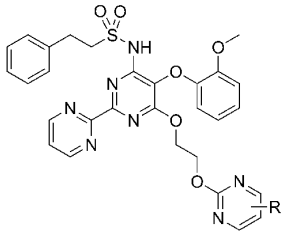
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

observed that such an additional pyrimidine ring improves the affinity for ET_A and ET_B significantly. Compound **1** derivative **18**, for instance, is about 10 times more potent on ET_A and about three times more active on ET_B than compound **1** itself. A similar trend was observed with the pair of phenylethane sulfonamides **19** and **20**. Interestingly, also the weakly active methane sulfonamide derivative **21** profits from the introduction of a pyrimidine ring, and the resulting compound **22** is almost 10 times more potent on both ET_A and ET_B than compound **21**. We therefore had a closer look at the structure–activity relationship (SAR) of this additional pyrimidine moiety. While various substituents were tolerated in the 5-position of the pyrimidine, substituents in positions 4 and/or 6 clearly hampered the compound's affinity for the ET receptors. This is illustrated with some examples of the phenylethane sulfonamide series compiled in Table 2. A comparable SAR, however, was observed with other scaffolds. Compared to the unsubstituted pyrimidine derivative **20**, the 5-methyl analogue **23** is less potent on both receptors. On the other hand, a 5-chloro (**24**), 5-bromo (**8**), 5-methoxy (**25**), 5-methylthio (**26**), and a 5-trifluoromethyl (**27**) substituent all led to a similarly improved affinity for ET_A. While the bromo-, methoxy-, and trifluoromethyl substituent improved the potency on ET_B only slightly, a 5-methylthio group increased the compound's affinity for this receptor significantly. The 5-cyclopropyl substitutent in **28** reproduced the profile of its unsubstituted analogue **20**. As illustrated with compound **29**, a 4,6-disubstitution pattern yielded only poorly active compounds.

On the one hand attaching a 5-bromo or a 5-methylthio-pyrimidine to the ethylene glycol moiety brought us closer to our goal of identifying endothelin antagonists more potent than compound **1**. On the other hand, these new compounds contain five aromatic rings and have a molecular weight well above 600 g/mol and therefore certainly do not qualify as lean molecules. In view of this, we carefully scrutinized the three substituents attached to positions 2, 4, and 5 of the core pyrimidine for possibilities to reduce the molecule's size. For these studies, we kept the 5-bromo-pyrimidine residue at the

UNITED THERAPEUTICS CORP., EX1006, page 361
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

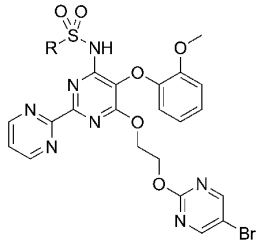
Table 2. Optimization of Pyrimidine[a]



compd	R	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
20	hydrogen	8.0	465
23	5-methyl	17.8	1501
24	5-chloro	2.8	461
8	5-bromo	2.2	216
25	5-methoxy	3.2	202
26	5-methylthio	1.1	42
27	5-trifluoromethyl	3.0	145
28	5-cyclopropyl	7.7	424
29	4,6-dimethoxy	4775	>10000

[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

Table 3. From Sulfonamides to Sulfamides[a]



compd	R	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
30	4-*tert*-butyl phenyl	1.5	19.3
31	phenyl	10.4	341
32	benzyl	73	3479
8	phenethyl	2.2	216
33	3-phenyl-propyl	6.7	377
34	methyl	113	1146
35	ethyl	14	460
36	*n*-propyl	9.4	566
37	*n*-butyl	4.3	552
38	benzyl-NH−	1.9	147
39	methyl-NH−	7.9	194
40	ethyl-NH−	9.9	655
41	*n*-propyl-NH−	3.8	322
42	*n*-butyl-NH−	1.7	167
43	*N*-benzyl-methyl-N-	7.0	457
44	morpholino	187	1474

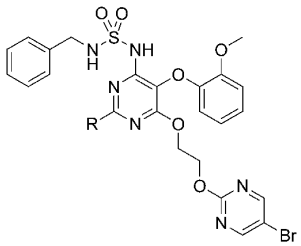
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. Note that compounds **8** and **30**−**37** represent sulfonamides, while compounds **38**−**44** represent sulfamides.

ethylene glycol constant. The compounds listed in Table 3 document the SAR of the sulfonamide part in position 4. Tables 4 and 5 illustrate the influence of the substituents in position 2 and 5, respectively.

In a first step, we removed the *tert*-butyl group attached to the benzene sulfonamide moiety. This resulted in a 10-fold loss of affinity for both ET receptors. When a CH_2 group was introduced as linker between the phenyl ring and the sulfur to give compound **32**, a further loss of affinity was observed. Interestingly, moving the phenyl two CH_2 units away from the sulfonamide moiety (compound **8**) restored the compound's affinity completely for the ET_A receptor and partially for the ET_B receptor. The affinity profile of phenyl-propane sulfonamide **33** is very similar to the one of the ethane analogue **32**. These observations combined with our aim to reduce molecular weight prompted us to study compounds lacking a phenyl ring in the sulfonamide part. Not unexpectedly though, the methane sulfonamide derivative **34** showed only moderate potency on the ET_A receptor. Much to our delight, however, the ethane sulfonamide **35** was almost as potent as the much bulkier phenylethane sulfonamide **8**. As shown with compounds **36** and **37**, the affinity for ET_A improves steadily with increasing length of the alkyl chain. No such trend was observed with the ET_B receptor. In a next step, we prepared a number of compounds wherein the sulfonamide moiety was replaced by a sulfamide group. As illustrated with compounds **38**−**43**, these novel sulfamide derivatives represent potent ET receptor antagonists. Only the morpholine derivative **44** shows some loss of affinity toward the two receptors. Compared to the corresponding sulfonamides, the sulfamides have almost identical affinity for the ET_A receptor (e.g., compare **8** with **38**, **35** with **39**, **36** with **40**, **37** with **41**). In contrast to the sulfonamide series, however, the IC_{50} value for the ET_B receptor improves with increasing length of the sulfamide alkyl chain. More importantly, the sulfamides show a trend toward improved potency on ET_B. This observation clearly moved the sulfamides into the focus of our interest. For the following studies, we selected sulfamide **38** as a reference compound. Hence, while keeping the benzyl sulfamide moiety constant, we prepared a series of analogues with different substituents in position 2 of the core pyrimidine. Several examples are compiled in Table 4. The pyrazine (**45**) and morpholine (**47**) derivatives showed an affinity profile almost identical to the one of the pyrimidine analogue **38**. The pyridine derivative **46**, on the other hand, lost potency, in particular on the ET_B receptor. As illustrated with compounds **48** and **49**, the loss in affinity is clearly more pronounced for the 2-cyclopropyl (**48**) and the 2-methoxy (**49**) substituted pyrimidine scaffolds. The 2-methoxy−ethoxy substituent in compound **50** led to a small loss in affinity for both receptors when compared to **38**. Interestingly, complete removal of the substituent in position 2 of the core pyrimidine (**51**) reproduced the affinity profile of compound **50**, suggesting that the contribution of the 2-substituent to the binding affinity is small. This encouraged us to further evaluate the sulfamide series with scaffolds lacking a substituent in position 2 of the core pyrimidine. We therefore prepared a number of 2-unsubstituted pyrimidine derivatives incorporating a selection of 5-substituents that were known to lead to potent ET receptor antagonists.[53−58] Some examples are compiled in Table 5. As shown with compounds **52** and **53**, a 3-methoxyphenoxy rather than a 2-methoxyphenoxy substituent led to an increase in potency on ET_A but left the affinity for ET_B unchanged. An unsubstituted phenyl ring directly bound to the core pyrimidine as in **54** had no impact on ET_A affinity

UNITED THERAPEUTICS CORP., EX1006, page 362
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 4. Optimization of Scaffold: 2-Substituent



compd	R	IC_{50} ET_A[a] [nM]	IC_{50} ET_B[a] [nM]
38	2-pyrimidinyl	1.9	147
45	2-pyrazinyl	2.1	166
46	4-pyridyl	3.4	561
47	4-morpholinyl	1.4	192
48	cyclopropyl	14	1082
49	methoxy	40	2490
50	2-methoxy-ethoxy	6.9	554
51	hydrogen	6.9	525

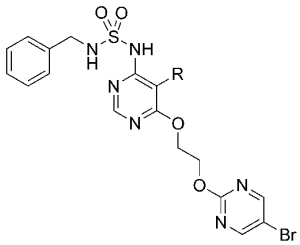
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

but caused a significant loss in the activity on ET_B. Introducing a methyl group (**55**), or a chlorine (**56**) or bromine (**57**) atom to the para position of the phenyl ring improved the compounds' affinity for both receptors significantly. Introducing even larger alkyl groups, as shown with compounds **58** and **59**, did not improve the compound's affinity any further. In fact, both compounds showed a clearly reduced potential to block the ET_B receptor.

In brief, the SAR studies discussed so far have shown that: (1) Introduction of a 5-bromo- or 5-methylthiopyrimidine to the ethylene glycol improves the compound's affinity for both ET receptors significantly (Table 1 and 2). (2) The bulky 4-*tert*-butyl benzene sulfonamide in compound **1** can be replaced by a benzyl or alkyl sulfamide moiety (Table 3). (3) Sulfamide derivatives are more potent on ET_B when compared to the corresponding sulfonamide analogues (Table 3). (4) A 2-substituent at the core pyrimidine is not mandatory to obtain potent ET antagonists (Table 4). (5) A 3-methoxyphenoxy, 4-methylphenyl, 4-chlorophenyl, or 4-bromophenyl residue attached to position 5 of the core pyrimidine leads to potent ET receptor antagonists (Table 5).

In Vivo Efficacy Assessment. In a next step, we assessed in vivo the oral efficacy of some of the most potent examples listed in Table 5. For this purpose, we measured the blood pressure lowering effect following oral administration by gavage of 3 mg/kg of each compound in conscious hypertensive Dahl salt-sensitive rats equipped with telemetry.[59−61] In this model, efficient blockade of the ET receptors results in a significant reduction of mean arterial blood pressure.[35] The pharmacological response was quantified by calculating the area between the curves (ABC) of the blood pressure recordings 24 h before and after treatment. As this experiment allowed for rapid and reliable assessment of the in vivo efficacy, we did not measure pharmacokinetic properties prior to pharmacological testing. In all experiments, the heart rate remained unaffected (data not shown). At an oral dose of 3 mg/kg, compound **1** maximally reduced mean arterial blood pressure by −7 ± 4 mmHg. The duration of action was about 15 h, which translated into an ABC of −88 mmHg·h (n = 8) (Table 5). A maximal reduction of mean arterial blood pressure by −30 ± 3 mmHg was achieved with a dose of 100 mg/kg. At this dose, compound **1** was active for about 72 h and displayed an ABC of −896 mmHg·h (n = 5).

Table 5. Optimization of Scaffold: 5-Substituent



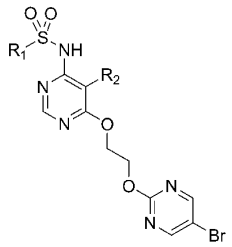
compd	R	IC_{50} ET_A[a] [nM][a]	IC_{50} ET_B[a] [nM][a]	max ΔMAP[b] [mmHg]	ABC[c] [mm Hg·h] (n)
1	*d*	45	202	−7 ± 4	−88 (8)
52	3-methoxyphenoxy	1.0	457	−10 ± 4	−245 (5)
53	2-chloro-5-methoxyphenoxy	1.4	712	−24 ± 5	−639 (5)
54	phenyl	6.8	5067	nd	nd
55	4-methylphenyl	0.7	441	nd	nd
56	4-chlorophenyl	1.4	506	−18 ± 6	−593 (6)
57	4-bromophenyl	1.6	461	−14 ± 3	−445 (6)
58	4-ethylphenyl	2.3	1264	nd	nd
59	4-isopropyl-phenyl	3.6	2474	nd	nd

[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. [b]Maximal mean arterial blood pressure reduction as extracted from the moving average over 6 h. [c]Area between curve (ABC) as calculated from the blood pressure recordings 24 h before and after administration of 3 mg/kg of the compound to conscious hypertensive Dahl salt-sensitive rats, max. ΔMAP = maximal reduction in mean arterial blood pressure; n = number of animals in the experiment, nd = not determined. [d]For the structure of compound **1**, see Figure 1.

dx.doi.org/10.1021/jm3009103 | *J. Med. Chem.* 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 363
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 6. Optimization of the Sulfamide Moiety[a]



compd	R_1	R_2	IC_{50} ET_A[b] [nM]	IC_{50} ET_B[b] [nM]	max ΔMAP[c] [mmHg]	ABC[d] [mm Hg·h] (*n*)
57	benzyl-NH−	4-bromophenyl	1.6	461	−14 ± 3	−445 (6)
60	methyl-NH−	4-bromophenyl	1.7	812	−21 ± 6	−1045 (5)
61	ethyl-NH−	4-bromophenyl	0.8	830	−20 ± 10	−598 (6)
17	*n*-propyl-NH−	4-bromophenyl	0.5	391	−25 ± 6	−922 (6)
62	*n*-butyl-NH−	4-bromophenyl	0.3	158	−16 ± 4	−443 (5)
63	cyclopropyl-NH−	4-bromophenyl	4.4	1474	nd	nd
64	*N*-benzyl-methyl-N−	4-bromophenyl	4.3	5208	nd	nd
65	morpholino	4-bromophenyl	2.8	2829	nd	nd
66	*n*-propyl-NH−	4-chlorophenyl	1.2	784	nd	nd
67	*n*-propyl-NH−	3-methoxyphenoxy	1.9	468	−15 ± 3	−391 (6)
68	*n*-propyl-NH−	6-chloro-3-methoxyphenoxy	0.4	208	−21 ± 5	−500 (6)
69	*n*-propyl	4-bromophenyl	2.2	3058	−25 ± 4	−1116 (6)
70	*n*-butyl	4-bromophenyl	1.1	2424	−22 ± 3	−734 (5)

[a]Note that compounds **17**, **57**, and **60**−**68** represent sulfamides, while compounds **69** and **70** are sulfonamides. [b]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. [c]Maximal mean arterial blood pressure reduction as extracted from the moving average over 6 h. [d]Area between curve (ABC) as calculated from the blood pressure recordings 24 h before and after administration of 3 mg/kg of the compound to conscious hypertensive Dahl salt-sensitive rats; max ΔMAP = maximal reduction in mean arterial blood pressure; *n* = number of animals in the experiment; nd = not determined.

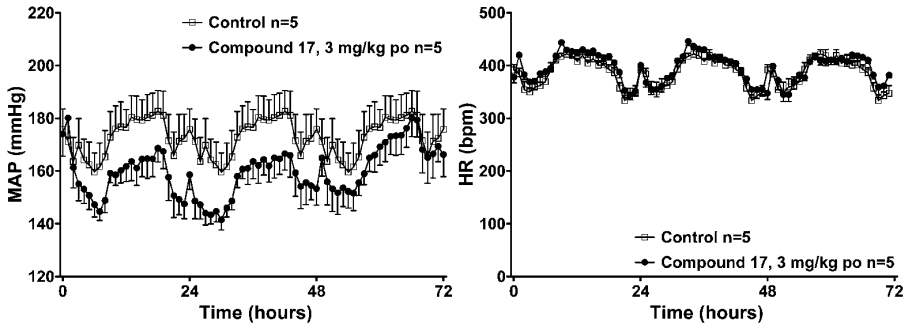


Figure 3. Mean arterial blood pressure (MAP, left) and heart rate (HR, right) recordings in conscious hypertensive Dahl salt-sensitive rats before (control) and after oral administration of 3 mg/kg of compound **17**. Results are expressed as mean ± SEM.

As apparent from the in vivo data given in Table 5, compounds incorporating a 3-methoxyphenoxy (**52**), 2-chloro-5-methoxyphenoxy (**53**), a 4-chlorophenyl (**56**), or a 4-bromophenyl (**57**) substituent at position 5 of the core pyrimidine clearly exceeded the in vivo activity of compound **1**. At this point, we decided to evaluate sulfamides with a 4-bromophenyl substituted pyrimidine scaffold in more detail. Several examples prepared for this study are listed in Table 6. For the ET_A receptor, the 4-bromophenyl derivatives reproduce the relative SAR observed with the corresponding 2-methoxyphenoxy analogues (Table 3) on a higher potency level (e.g., **39** vs **60**, **40** vs **61**, **44** vs **65**), and several compounds reach affinities below 1 nM. With respect to ET_B, the relative SAR between the 4-bromophenyl derivatives and the 2-methoxyphenoxy-analogues is again similar. However, this time the bromo-phenyl derivatives in Table 6 are often less potent when compared to their analogues in Table 3 (e.g., **38** vs **57**, **43** vs **64**). Notable exceptions are compounds **17** and **62**, which both retain their ET_B affinity.

When we tested the sulfamides of Table 6 in our rat model of hypertension, compounds incorporating a rather small alkyl sulfamide showed excellent in vivo activity (e.g., **60**, **61**, **17**). The propyl-sulfamide **17** emerged as a particularly interesting compound as it combined high in vivo efficacy with high potency on ET_B. We therefore extended our study to the three propyl sulfamides incorporating a 4-chlorophenyl (**66**), a 3-methoxyphenoxy (**67**), or a 6-chloro-3-methoxyphenoxy (**68**) substituent in position 5 of the core pyrimidine (Table 6). The in vitro activity of compound **66** was inferior to the one of compound **17** as it was clearly less potent on ET_B. While the 3-

UNITED THERAPEUTICS CORP., EX1006, page 364
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

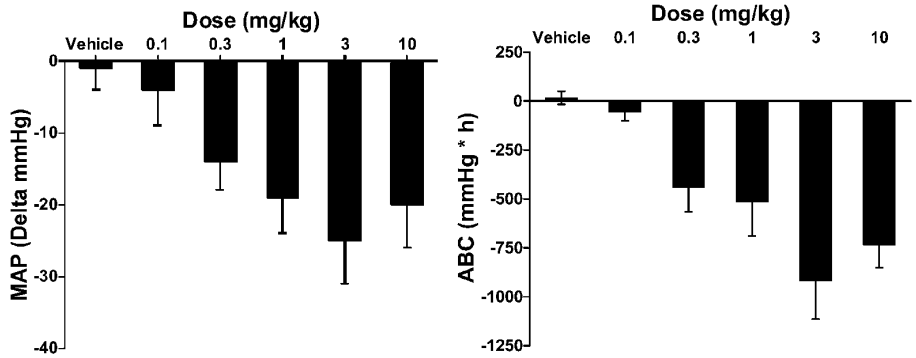


Figure 4. Dose–response curve of mean arterial blood pressure (MAP) reduction and area between curves (ABC) in hypertensive Dahl salt-sensitive rats after oral administration of compound **17** in 5% arabic gum. Results are expressed as mean ± SEM.

methoxyphenoxy derivative **67** was only slightly less potent than **17**, the chloro substituted analogue **68** was more potent on ET_B. However, both compounds **67** and **68** showed a clearly lower activity in vivo. A comparison of sulfamide **17** with sulfonamides **69** and **70** confirmed our earlier finding that the sulfamides present a significantly higher affinity for the ET_B receptor. In our context, the sulfonamides **69** and **70** are therefore clearly less attractive despite their high in vivo activity in the Dahl salt-sensitive rat model of hypertension (Table 6).

In brief, the *n*-propylsulfamide derivative **17**, later named macitentan,[62] fulfilled the requirements we set forth at the beginning of our discovery program. Sulfamide **17** is highly potent on the ET_A receptor with significant affinity for the ET_B receptor and maximally reduces mean arterial blood pressure for at least 60 h at an oral dose of 3 mg/kg (Figure 3). Following a dose–response experiment, maximal reduction of mean arterial blood pressure by −25 ± 6 mmHg was reached with a dose of 3 mg/kg (Figure 4). No change in heart rate was observed over the range of 1–100 mg/kg in conscious Dahl salt-sensitive rats (Figure 3, data not shown). In a multiple dose experiment, Dahl salt-sensitive rats were treated for five consecutive days with 1 mg/kg/day of **17** (Figure 5). Mean arterial blood pressure was stably reduced by −20 mmHg over the whole treatment period and returned to baseline about 48 h after the last dose was given. No signs of tachyphylaxis were observed, and no rebound effect manifested at the end of the study as blood pressure values returned to baseline.

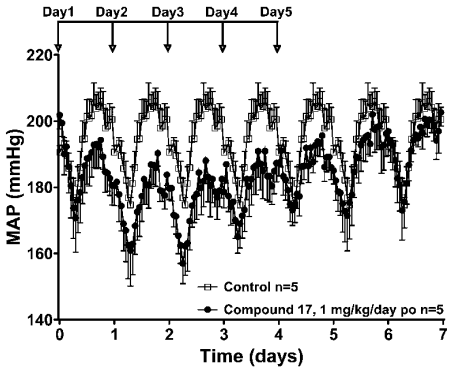


Figure 5. Mean arterial blood pressure (MAP) recordings of a repeated dose experiment administering 1 mg/kg/day of compound **17** over five consecutive days to hypertensive Dahl salt-sensitive rats equipped with telemetry (ABC = 1842 mmHg·h). Results are expressed as mean ± SEM.

In view of the excellent pharmacodynamic behavior of compound **17**, it came as no surprise that **17** also showed favorable pharmacokinetic properties (Table 7). In an iv experiment with male Wistar rats, the compound showed a low plasma clearance of 6.7 mL/min·kg translating into a half-life of 5.1 h. The volume of distribution reached 1.8 L/kg, indicating that the compound is distributing well into tissues. At an oral dose of 10 mg/kg, compound **17** reached a peak plasma concentration of 1670 ng/mL at 6 h after administration. Oral bioavailability was 69%. A similar pharmacokinetic behavior was found in the dog, emphasizing the compound's attractiveness for further development. In the dog, compound **17** was rapidly (T_{max} = 2 h) and almost completely (F = 87%) absorbed and reached plasma concentrations close to 5000 ng/mL after oral administration of 10 mg/kg. Clearance and half-life are comparable in rat and dog.

In the course of our PK studies we discovered that compound **17** is metabolized to the depropylated sulfamide **71** (Figure 6). This compound represents a major metabolite reaching plasma exposure levels 4–5 times higher than that of **17**. Sulfamide **71** binds to the ET_A and ET_B receptors with IC_{50} values of 3.4 and 987 nM, respectively and therefore clearly adds to the pharmacological activity of the parent compound **17**.[62] As we learned later, metabolite **71** is also formed in humans.[63] Interestingly, oral administration of 10 mg/kg of the butyl analogue **62** to Wistar rats also led to significant plasma concentrations (C_{max} = 4100 ng/mL at 6 h after administration) of sulfamide **71**.

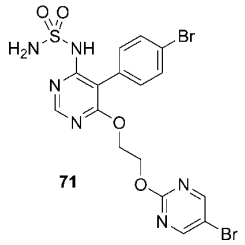
In 10.9% of the patients treated with compound **1**, a transient, dose dependent increase in serum liver aminotransferase levels of >3 times the upper limit of normal is observed.[64−66] Mechanistically, this observation has been attributed to the ability of compound **1** to inhibit bile salt transport in hepatocytes, eventually leading to intrahepatic cholestasis.[37] Minimizing the interaction of a potential follow-up compound with hepatic bile acid transport has therefore been a further goal of our optimization efforts. Several compounds have been assessed for their potential to interact with bile salt transport in a rat model,[37] and compound **17** showed no sign of bile salt transport inhibition in this model (data not shown).

UNITED THERAPEUTICS CORP., EX1006, page 365
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 7. PK Parameters of 17 in Male Wistar Rats and Male Beagle Dogs

species	iv dose[a] [mg/kg]	AUC_{0-inf} [ng h/mL]	CL [mL/min·kg]	Vss [L/kg]	$t_{1/2}$ [h]	oral dose[b] [mg/kg]	AUC_{0-inf} [ng h/mL]	C_{max} [ng/mL]	T_{max} [h]	F [%]
Wistar rat (n = 5)	1	2680 ± 730	6.7 ± 2.1	1.8 ± 0.9	5.1 ± 1.9	10	18500 ± 8100	1670 ± 371	6.0	69
beagle dog (n = 3)	1	3170 ± 520	5.4 ± 1.0	0.9 ± 0.2	4.1 ± 0.4	10	27500 ± 6500	4590 ± 2540	2.0	87

[a]Wistar rat: solution in 50 mM aqueous tris(hydroxymethyl)methylamine (Tris) pH 8.3 buffer containing 45% PEG400; beagle dog: solution in 25% *N*-methylpyrrolidone (NMP), 25% PEG400, 50% 50 mM aqueous Tris pH 8.3 buffer. [b]Wistar rat: suspension in 7.5% aqueous modified gelatin; beagle dog: solution in PEG400.



71

Figure 6. Stucture of sulfamide **71**, a major metabolite of compound **17** in Wistar rats and Beagle dogs.

CONCLUSIONS

In conclusion, starting from the structure of compound **1**, we have discovered a novel series of highly potent ET receptor antagonists. While these novel compounds are still based on a pyrimidine core, the *tert*-butyl benzene sulfonamide part of compound **1** has been replaced by a series of simple alkyl sulfamide moieties. When compared to the corresponding sulfonamides, these novel sulfamides are characterized by an enhanced affinity for the ET_B receptor, rendering them a particularly interesting class of novel ET receptor antagonists. In addition, many of these sulfamides show high oral efficacy in reducing arterial blood pressure in conscious hypertensive Dahl salt-sensitive rats. In vivo dealkylation of the alkyl sulfamide moiety in compounds **17** and **62**, for instance, to the pharmacologically active sulfamide **71** is another interesting feature of the sulfamide class as it leads to sustained pharmacological activity.

Sulfamide **17** emerged as a highly attractive candidate for further studies and can be characterized as a potent ET_A receptor antagonist with significant affinity for the ET_B receptor. In rat and dog models, the compound is well absorbed, distributes well into tissue, and is slowly cleared, suggesting that it is suitable for once daily dosing in humans. Recently published data on a phase I clinical trial with compound **17** confirm these expectations.[63] In hypertensive Dahl salt-sensitive rats, **17** efficiently and dose dependently reduced the arterial blood pressure. More detailed studies with sulfamide **17** on its tissue penetration and ability to block the ET_A and ET_B receptor in vivo have been described in a separate publication.[62] In a rat model, compound **17** did not increase plasma bile salt concentrations. Compound **17** successfully completed a phase III clinical trial for pulmonary arterial hypertension recently.[67] A phase IIIb clinical trial for digital ulcers[68,69] and a phase I/Ib trial for recurrent glioblastoma[70] are currently ongoing.

EXPERIMENTAL SECTION

Chemistry. All reagents and solvents were used as purchased from commercial sources (Sigma-Aldrich Switzerland, Lancaster Synthesis GmbH, Germany, Acros Organics USA). Moisture sensitive reactions were carried out under an argon atmosphere. Progress of the reactions was followed either by thin-layer chromatography (TLC) analysis (Merck, 0.2 mm silica gel 60 F_{254} on glass plates) or by LC-MS. LC-MS: UltiMate 3000 RS pump, UltiMate 3000 column compartment (40 °C), UltiMate 3000 RS DAD, MSQplus (all Dionex, Switzerland), Sedex 85 ELSD (Sedere, VWR Germany). Column: Zorbax SB-AQ, 5 μm, 120 Å, 4.6 mm × 50 mm (Agilent). Gradient: 5–95% acetonitrile in water containing 0.04% of trifluoroacetic acid, within 1 min. Flow: 4.5 mL/min. Or LC-MS*: Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT. Colum: Gromsil ODS4, 3 μm, 120 Å; 2 mm × 30 mm. Gradient: 0–100% acetonitrile in water containing 0.05% formic acid, within 6 min. Flow: 0.45 mL/min; t_R is given in min. Purity of the target compounds was confirmed on two additional columns: on a Waters Atlantis T3, 5 μm, 4.6 mm × 30 mm, eluting with a gradient of 5–95% of acetonitrile in water containing 0.04% of trifluoroacetic acid; and on a Waters XBridge C18, OBD, 5 μm, 4.6 mm × 50 mm (Waters, Switzerland), eluting with a gradient of 5–95% of acetonitrile in water containing 13 mM of NH_3. According to these three LC-MS analyses, all compounds showed a purity >95% (UV at 230 nm), and about 80% of the compounds showed a purity >98%. Purity and identity was further confirmed by NMR spectroscopy. HR-LC-MS: analytical pump, Waters Acquity Binary, Solvent Manager. MS: SYNAPT G2MS, source temperature 150 °C, desolvatation temperature 400 °C, desolvatation gas flow 400 L/h. Cone gas flow: 10 L/h. Extraction cone: 4 RF. lens: 0.1 V. Sampling cone: 30. Capillary: 1.5 kV. High resolution mode. Gain: 1.0. MS function: 0.2 s per scan, 120–1000 amu in full scan, centroid mode. Lock spray: leucine enkephalin 2 ng/mL (556.2771 Da) scan time 0.2 s with interval of 10 s and average of five scans. DAD: Acquity UPLC PDA detector. Column: Acquity UPLC BEH C18 1.7 μm 2.1 mm × 50 mm from Waters, thermostatted in the Acquity UPLC column manager at 60 °C. Eluents: water + 0.05% formic acid; B, acetonitrile + 0.05% formic acid. Gradient: 2–98% B over 3.0 min. Flow: 0.6 mL/min. Detection: UV 214 nm and MS, t_R is given in min. Prep HPLC: Waters XBridge Prep C18, 5 μm, OBD, 19 mm × 50 mm, gradient of acetonitrile in water containing 0.4% of formic acid, flow 75 mL/min. Melting points were determined by differential scanning calorimetry (DSC) using a DSC822e/400 instrument and the HSS7 sensor from Mettler Toledo, Switzerland. The sample is weighed in a 40 μL aluminum crucible which is open under a flow of 15 mL/min of nitrogen during the experiment. The scan goes from 20 to 320 °C at a rate of 5 K/min. The peak temperature of the melting endotherm was determined with the STARe software and was assigned to the melting point (mp). NMR spectroscopy: NMR spectra were recorded on a Varian Mercury 300VX spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) or Bruker Avance II, 400 MHz UltraShield, ^{1}H (400 MHz), ^{13}C (100 MHz); chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), h (hextet), hept (heptuplet) or m (multiplet). X-ray diffraction: Crystals of **17** were mounted on a Bruker Nonius diffractometer equipped with a CCD detector and reflections were measured using monochromatic Mo Kα radiation. The structure was solved by direct methods using SIR92, refinement was performed with CRYSTALS. Full matrix least-squares refinement was performed with anisotropic temperature factors for all atoms except hydrogen which were included at calculated positions with isotropic temperature factors. Coordinates,

UNITED THERAPEUTICS CORP., EX1006, page 366
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

anisotropic temperature factors, bond lengths, and angles will be deposited with the Cambridge Crystallographic Data Centre.

Endothelin Receptor Inhibition. Binding assays were performed in 96-well plates with CHO membranes containing the recombinant ET_A or ET_B receptors in 200 μL of 50 mM Tris-HCl, 25 mM $MnCl_2$, 1 mM EDTA pH 7.4, 0.5% BSA, 2.5% DMSO. The wells containing 0.5 μg/well of ET_A membranes or 0.2 μg/well of ET_B membranes were incubated for 2 h at RT with 15 pM [^{125}I]ET-1 (10000 cpm) in the presence or absence of test substances. Minimum and maximum binding was derived from samples with and without 1 μM of unlabeled ET-1, respectively. After the 2 h incubation period, the membranes were filtered through GF/C filterplates (MultiScreen MAHFC 1H60 from Millipore), which had been pre-equilibrated with binding buffer, using cold 50 mM Tris HCl, 0.1% BSA pH 7.5. After drying of the filterplates, 25 μL of scintillation cocktail (MicroScint 20, Perkin-Elmer) were added to each well and the filterplates were counted in a microplate counter (TopCount, Canberra Packard S.A. Zürich, Switzerland). IC_{50} values were calculated as the concentration of antagonist inhibiting 50% of the specific binding of ET-1. Two reference compounds were tested: BQ-123, a specific ET_A antagonist, and sarafotoxin 6c (Bachem, Switzerland), a specific ET_B antagonist. For these reference inhibitors, the following IC_{50} values were found (geometric mean values): ET_A mb, 20.5 nM (n = 13) for BQ-123 and >100 nM (n = 10) for Sarafotoxin; ET_B mb, 0.208 nM (n = 12) for Sarafotoxin and >1000 nM (n = 12) for BQ-123.

Telemetric in Vivo Studies.[59−61] In vivo efficacy of the compounds was assessed by oral administration of 3 mg/kg of the compound suspended in 5% arabic gum to female hypertensive Dahl salt-sensitive rats equipped with a telemetric system recording the arterial blood pressure and heart rate. For both of these parameters, each rat served as its own control by using the data of the last 24 h before treatment. An area between curve (ABC) was calculated between the control and the treatment period to assess the compound's efficacy. Maximal mean arterial blood pressure reduction was extracted from the moving average over 6 h of the blood pressure recordings.

Pharmacokinetics in the Rat. The pharmacokinetic profile was determined in the male Wistar rat (n = 5). For this purpose, compound **17** was formulated as a solution in 50 mM aqueous tris(hydroxymethyl)methylamine (Tris) pH 8.3 buffer containing 45% PEG400 for intravenous administration at a dose of 1.0 mg/kg, and as a microsuspension in 7.5% aqueous modified gelatin for oral dosing at 10 mg/kg. Blood samples were taken at regular time intervals over a period of 24 h from a preimplanted catheter, and plasma was generated by centrifugation at 4000 rpm at 4 °C. Plasma concentrations were determined using a specific and sensitive LC-MS/MS method with a limit of quantification of 1.5 ng/mL.

Pharmacokinetics in the Dog. The pharmacokinetic profile of compound **17** was determined in male beagle dogs (n = 3). The compound was administered orally at a dose of 10 mg/kg as a solution in PEG400 and intravenously at a dose of 1 mg/kg as a solution in 25% *N*-methylpyrrolidone (NMP), 25% PEG400, 50% 50 mM aqueous Tris pH 8.3 buffer.

Potassium (Phenethylsulfonyl)amide (4).[71] To a vigorously stirred solution of *N*-chlorosuccinimide (38.6 g, 289 mmol) in dichloromethane (300 mL) and water (150 mL), 2-phenyl-ethyl-mercaptane (10.0 g, 72.3 mmol) was added. The mixture became slightly warm (30 °C). The resulting suspension was stirred at rt for 3 h. The solvent was decanted, and the remaining slurry was extracted twice with dichloromethane (2 × 200 mL). The organic extracts were washed twice with satd aq $NaHCO_3$ solution and water, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was suspended in heptane:ethyl acetate 10:1, filtered, and washed with additional ethyl acetate/hexane. The filtrate was concentrated, and the crude product was purified by colum chromatography on silica gel eluting with heptane:ethyl acetate 10:1 to give 2-phenyl-ethane sulfonylchloride (8.25 g, 56%) as a pale-beige oil; R_f (silica gel, heptane:ethyl acetate 10:1) 0.32. This material (8.25 g, 40.3 mmol) was dissolved in THF (50 mL), and a solution of satd aq NH_3 (10 mL) was slowly added at −20 °C. The mixture was stirred at rt for 16 h before it was neutralized with 25% aq HCl. The organic solvent was evaporated, and the remaining residue was diluted with water (100 mL) and extracted four times with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 2-phenyl-ethane sulfonamide (6.21 g, 83%) as a pale-yellow solid. LC-MS: t_R = 0.58 min, $[M + H]^+$ = not detectable. To a solution of this material (6.21 g, 33.5 mmol) in methanol (60 mL), potassium *tert*-butylate (3.76 g, 33.5 mmol) was added. The mixture was stirred until a clear solution formed. The mixture was concentrated and the remaining residue was triturated with diethyl ether, filtered, and dried to give **4** (6.67 g, 89%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 7.18−7.32 (m, 5 H), 3.05−3.11 (m, 2 H), 2.93−2.99 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ 140.1, 129.0, 128.8, 126.7, 56.8, 30.9.

4,6-Dichloro-5-(2-methoxyphenoxy)-2,2′-bipyrimidine (3). Prepared as described in the literature.[39,41] LC-MS: t_R = 0.79 min, $[M + H]^+$ = 349.04. ^{1}H NMR ($CDCl_3$): δ 9.05 (d, J = 4.9 Hz, 2 H), 7.47 (t, J = 4.9 Hz, 1 H), 7.13 (td, J_t = 8.0 Hz, J_d = 1.5 Hz, 1 H), 7.00 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1 H), 6.90 (td, J_t = 8.0 Hz, J_d = 1.4 Hz, 1 H), 6.79 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 160.2, 158.2, 156.6, 155.5, 149.3, 145.0, 144.6, 125.0, 121.8, 121.0, 116.9, 113.0, 56.2.

***N*-(6-Chloro-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenylethane-sulfonamide (5).** A solution of **3** (2.20 g, 6.30 mmol) and **4** (3.10 g, 13.86 mmol) in DMF (50 mL) was stirred at rt for 16 h. About half of the solvent was removed under reduced pressure before the mixture was diluted with diethyl ether (50 mL). A 10% aqueous solution of citric acid (50 mL) was added. The beige suspension that formed was filtered, the collected solid was washed with water (30 mL) and diethyl ether (30 mL), and dried under high vacuum at 50 °C to give **5** (2.79 g, 89%) as a beige powder. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 497.81. ^{1}H NMR (DMSO-d_6): δ 8.99 (d, J = 4.9 Hz, 2 H), 7.64 (t, J = 4.9 Hz, 1 H), 7.20−7.26 (m, 4 H), 7.14−7.20 (m, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.61 (s br, 1 H), 3.83 (s, 3 H), 2.82−2.97 (m, 2 H).

***N*-(6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenyl-ethanesulfonamide (7).** At rt, potassium *tert*-butoxide (6.88 g, 6.03 mmol) was added portionwise to a solution of **5** (304 mg, 0.60 mmol) in ethylene glycol (10 mL) and DME (2 mL). The reaction mixture was heated to reflux for 17 h and then cooled to rt before being poured into 10% aq citric acid solution (25 mL). The mixture was extracted twice with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to give sufficiently pure **7** as an off-white solid to be used without further purification. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 524.05. ^{1}H NMR ($CDCl_3$): δ: 3.21−3.28 (m, 2 H), 3.91−3.95 (m, 2 H), 3.98 (s, 3 H), 4.29−4.38 (m, 2 H), 4.66−4.70 (m, 2 H), 6.95 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.3 Hz, 1 H), 7.13−7.30 (m, 7 H), 7.42 (t, J = 4.8 Hz, 1 H), 8.48 (s br, 1 H), 8.93−8.99 (m, 2 H).

***N*-(6-(2-((5-Bromopyrimidin-2-yl)oxy)ethoxy)-5-(2-methoxy-phenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenylethanesulfonamide (8).** To a suspension of NaH (29 mg, 0.72 mmol, 60% in mineral oil) in THF (2 mL) and DMF (2 mL), alcohol **7** (150 mg, 0.29 mmol) was added. The mixture was stirred at rt for 5 min before 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) was added. The mixture was stirred at 70 °C for 4 h before another portion of 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) and NaH (29 mg, 0.72 mmol) was added. Stirring was continued at 70 °C for 22 h before another portion of 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) and NaH (29 mg, 0.72 mmol) was added. Stirring was continued for further 3 h before the mixture was cooled to rt and poured into 10% aq citric acid solution (75 mL). The mixture was extracted twice with ethyl acetate (2 × 50 mL). The combined extracts were washed with 10% aq citric acid solution (50 mL) and concentrated. The crude product was purified on prep TLC plates (silica gel, 0.5 mm) using ethyl acetate:methanol:7 N NH_3 in methanol 8:2:1 to give **8** (84 mg, 43%) as a pale yellow solid; R_f (silica gel, ethyl acetate:methanol:7 N NH_3 in methanol 8:2:1) 0.68. LC-MS: t_R = 0.93 min, $[M + H]^+$ = 680.01. ^{1}H NMR ($CDCl_3$) (2 conformers 1:2): δ 8.88−8.96 (m, 2 H), 8.49 (s, 1.33 H), 8.43 (s, 0.67 H), 7.50 (t, J = 5.0 Hz, 0.33 H), 7.35−

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 367
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

7.42 (m, 0.67 H), 7.16–7.27 (m, 3.33 H), 7.01–7.15 (m, 2 H), 6.88–6.98 (m, 1.34 H), 6.79–6.87 (m, 1.67 H), 6.72–6.78 (m, 0.33 H), 5.02–5.07 (m, 0.67 H), 4.96–5.02 (m, 1.33 H), 4.72–4.77 (m, 0.67 H), 4.66–4.71 (m, 1.33 H), 4.18–4.34 (m, 1.33 H), 3.96 (s, 2 H), 3.90 (s, 1 H), 3.11–3.25 (m, 1.33 H), 2.91–3.00 (m, 0.67 H), 2.66–2.73 (m, 0.67 H). ^{13}C NMR ($CDCl_3$) (2 conformers): δ 163.48, 163.47, 161.9, 161.8, 159.5, 159.4, 157.7, 157.6, 157.5, 155.9, 150.5, 149.7, 149.4, 146.7, 145.8, 138.6, 137.7, 128.58, 128.55, 128.4, 128.2, 127.3, 126.7, 126.2, 125.2, 122.9, 122.5, 121.5, 121.2, 120.8, 115.3, 113.0, 112.4, 112.1, 112.0, 66.1, 66.0, 65.1, 64.9, 56.5, 56.0, 55.8, 55.5, 29.7, 29.6.

Potassium (*N*-Propylsulfamoyl)amide (13). Chlorosulfonyl isocyanate (**9**, 28.3 g, 0.2 mol) was dissolved in DCM (100 mL) and cooled to 0 °C before a solution of *tert*-BuOH (18.8 mL; 0.2 mol) in DCM (100 mL) was added over 30 min. Stirring was continued without cooling for additional 30 min. The mixture was then carefully added over 1 h to a solution of *n*-propylamine (16.5 mL, 0.2 mol) and triethylamine (42 mL, 0.3 mol) in DCM (400 mL) at 0 °C. Stirring was continued without cooling for additional 16 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in EtOAc (1 L) and washed with water (100 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give **11**. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7 Hz, 3 H), 1.51 (s, 9 H), 1.62 (m, 2 H), 3.04 (q, J = 6 Hz, 2 H), 5.12 (t br, J = 5 Hz, 1 H), 7.17 (s br, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.8, 28.4, 46.0, 84.1, 150.3. The residue was dissolved in dioxane (100 mL) followed by the addition of HCl in dioxane (4M; 250 mL). Stirring was continued for 4 h at rt. The solvent was evaporated under reduced pressure, and the residue was dried under HV to give sulfamide **12**. ^{1}H NMR (DMSO-d_6; 300 MHz; Varian): δ 0.87 (t, 3H), 1.43 (m, 2H), 2.81 (q, 2H), 3.09 (m, 1H; NH), 6.42 (s, 2H; NH_2). ^{13}C NMR($CDCl_3$): δ 11.6, 23.1, 45.7. The residue was dissolved in MeOH (200 mL), and KOtBu (22.4 g; 0.2 mol) was added. The solvent was removed under reduced pressure. The residue was taken up in diethylether (500 mL), and the precipitate was filtered off, washed with cold ether, and dried at HV to give potassium (*N*-propylsulamoyl)amide (**13**) (32.4 g, 92%) as an off-white powder.

5-(4-Bromophenyl)-4,6-dichloropyrimidine (14).[42] To a solution of 4-bromophenylacetic acid (73.9 g, 0.34 mol) in methanol (400 mL), thionyl chloride (49.05 g, 30 mL, 0.41 mol) was added dropwise while the temperature of the reaction mixture was kept at 0–5 °C. Upon complete addition, the cooling was removed and the mixture was allowed to warm to rt. Stirring was continued for 3 h before the solvent was removed in vacuo. The yellow oil was dissolved in benzene and evaporated. The residue was dissolved in ethyl acetate and washed with brine, 2 N aq Na_2CO_3, and again brine. The organic extract was dried over $MgSO_4$ and evaporated and dried under high vacuum at 85 °C for 30 min to give 4-bromophenylacetic acid methyl ester (74.9 g, 95%) as a yellow oil. LC-MS: t_R = 0.93 min, $[M + H]^+$ = not detectable. ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 3H), 3.67 (s, 2H), 7.22 (d, J = 8.5, 2H), 7.50 (d, J = 8.5, 2H). ^{13}C NMR ($CDCl_3$): δ 40.9, 52.5, 121.4, 131.2, 131.9, 133.1, 171.6.

NaH (24.0 g, 0.82 mol, 60% in mineral oil) was suspended twice in THF (75 mL), and the solvent was decanted. The remaining slurry was diluted with THF (500 mL) and heated to 35–40 °C. A solution of 4-bromophenylacetic acid methyl ester (74.9 g, 0.33 mol) in THF (200 mL) was carefully added dropwise. Gas evolution started after about half of the phenylacetic acid ester had been added and the mixture became slightly warm. The addition was continued at 45 °C. Upon completion of the addition, stirring was continued at 40 °C for 5 min before the mixture was allowed to cool to rt. The evolution of gas had stopped before dimethylcarbonate (117.9 g, 1.31 mol) was added dropwise. Evolution of gas started, and the mixture became warm (32 °C). Upon completion of the addition, stirring of the mixture was continued for 24 h before it was cooled to 0 °C and acidified by adding 25% aq HCl (100 mL) and diluted with water (150 mL). The organic solvent was removed under reduced pressure, and the remaining aqueous mixture was extracted three times with ethyl acetate (3 × 200 mL). The organic extracts were washed with 1 N aq HCl and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was crystallized from diethyl ether/hexane. The solid material was collected, washed with cold diethyl ether/hexane, and dried under high vacuum to give 2-(4-bromophenyl)-malonic acid dimethyl ester (74.1 g, 79%) as beige crystals; mp 76–77 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.7, shows decomposition. LC-MS: this compound is not stable under HPLC conditions. ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 6 H), 4.61 (s, 1 H), 7.25–7.30 (m, 2 H), 7.46–7.51 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 53.4, 57.3, 122.9, 131.2, 131.7, 132.0, 168.2.

A solution of 2-(4-bromophenyl)-malonic acid dimethyl ester (11.73 g, 40.9 mmol) in methanol (100 mL) was added at 0 °C to a solution of sodium (2.83 g, 0.118 mmol) in methanol (100 mL). The mixture was stirred for 18 h at rt before formamidine hydrochloride (4.10 g, 50.9 mmol) was added. The suspension was stirred at rt for 4 h. The solvent was removed, and the residue was suspended in 10% aq citric acid (100 mL) and stirred for 10 min. The white precipitate was collected, washed with 10% aq citric acid, water, evaporated three times from cyclohexane, and dried under high vacuum at 40 °C to give 5-(4-bromophenyl)-pyrimidine-4,6-diol (9.90 g, 91%) as a pale-beige powder; R_f (silica gel, heptane:ethyl acetate 1:1) at start. LC-MS: t_R = 0.52 min, $[M + H]^+$ = 267.08. ^{1}H NMR (DMSO-d_6): 7.43–7.48 (m, 2 H), 7.50–7.55 (m, 2 H), 8.13 (s, 1 H), 12.1 (s br, 2 H). ^{13}C NMR (DMSO-d_6): δ 101.4, 119.3, 130.6, 132.9, 133.2, 148.7, 163.2.

To a suspension of 5-(4-bromophenyl)-pyrimidine-4,6-diol (43.0 g, 0.16 mmol) in $POCl_3$ (500 mL) was carefully added *N*,*N*-dimethylaniline (50 mL). The mixture was heated to 130 °C for 2 h. The dark-brown solution was evaporated, and the residue was dissolved in dichloromethane (200 mL). Water (500 mL) was slowly added, and the mixture was stirred at rt for 30 min before the organic phase was separated. The aqueous phase was extracted two more times with dichloromethane. The organic extracts were washed with water and 1 N aq HCl, treated with charcoal, dried over $MgSO_4$, filtered, and evaporated. The product was purified by crystallization from 2-propanol. The crystals were collected, washed with cold 2-propanol and dried under high vacuum to give **14** (39.8 g, 81%) as beige crystals; mp 100–101 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.79. LC-MS: t_R = 0.92 min, $[M + H + CH_3CN]^+$ = 344.0. ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1 H), 7.68 (dt, J_d = 8.9 Hz, J_t = 2.4 Hz, 2 H), 7.22 (dt, J_d = 9.0 Hz, J_t = 2.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 124.1, 131.0, 131.7, 132.3, 157.1, 161.4.

***N*-5-(4-Bromophenyl)-6-chloro-4-pyrimidinyl-*N*′-propylsulfamide (15).** To a solution of **14** (760 mg; 2.50 mmol) in DMSO (5 mL), the sulfamide potassium salt **13** (529 mg; 3.00 mmol) was added. The mixture was stirred at rt for 48 h, diluted with brine (25 mL), and extracted three times with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was crystallized form methanol to give **15** (706 mg, 69%) as a white solid; R_f (silica gel, heptane:ethyl acetate 1:1) 0.49. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 404.98. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, J = 7.6 Hz, 3 H), 1.50–1.66 (m, 2 H), 2.94–3.03 (m, 2 H), 5.52 (s br, 1 H), 6.90 (s br, 1 H), 7.16–7.21 (m, 2 H), 7.68–7.74 (m, 2 H), 8.65 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 118.6, 125.0, 128.9, 131.2, 133.6, 156.6, 157.0, 159.9.

***N*-5-(4-Bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl-*N*′-propylsulfamide (16).** Ethylene glycol (58.7 g, 53 mL; 946 mmol) was dissolved in dimethoxyethane (80 mL), and KOtBu (8.80 g; 78 mmol) was added. The temperature rose to 40 °C. After stirring for 10 min, monochloride **15** (10.55 g; 26 mmol) was added and stirring was continued at 100 °C for 70 h. The reaction mixture was carefully added to a 1:1 mixture of water:10% aq citric acid solution. The product was extracted with ethyl acetate (2 × 120 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The crude product was purified by flash column chromatography (silicagel, heptanes:ethyl acetate 1:1) to give alcohol **16** (9.65 g, 86%) as a white solid; R_f (silica gel, heptane:ethyl acetate 1:1) 0.20. LC-MS: t_R = 0.88 min, $[M + H]^+$ = 430.98. ^{1}H NMR ($CDCl_3$): δ 0.95 (t; J = 7.6 Hz, 3 H), 1.60 (h, J = 7.6 Hz, 2 H), 2.98 (t, J = 7.0 Hz, 2 H), 3.82–3.86 (m, 2 H), 4.47–4.51 (m, 2 H), 5.70 (s br, 1 H), 7.13–7.22 (m, 2 H), 7.61–7.67 (m, 2 H), 8.48 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 61.9, 69.8, 104.8, 123.8, 128.1, 131.6, 133.2, 155.9, 156.4, 166.6.

UNITED THERAPEUTICS CORP., EX1006, page 368
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

***N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]-ethoxy]-4-pyrimidinyl]-*N*′-propylsulfamide (17).** Sodium hydride (1.67 g, 69.6 mmol, 55% in mineral oil) was suspended twice in hexane (10 mL), and the hexane was discarded. The remaining slurry was suspended in THF (200 mL), and **16** (10.0 g, 23.2 mmol) was added in portions. The mixture was stirred for 15 min and diluted with DMF (40 mL) before 5-bromo-2-chloropyrimidine (5.38 g; 27.8 mmol) was added. The reaction mixture was heated to 60 °C, and stirring was continued for 2 h. The mixture was poured into 10% aq citric acid solution (250 mL), and the product was extracted twice with ethyl acetate (2 × 300 mL). The combined organic extracts were washed twice with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by crystallization from methanol (100 mL) to give **17** (11.99 g, 88%) as a white powder; mp 135–136 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.44. LC-MS: t_R = 0.79 min, $[M + H]^+$ = 588.86 (major isotope). HR-LC-MS: t_R = 1.96 min; $(m + H)/z$ = 586.9711, found = 586.9714. ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 2 H), 8.49 (s, 1 H), 7.58–7.63 (m, 2 H), 7.16–7.21 (m, 2 H), 6.88 (s, 1 H), 5.61 (t, J = 6.2 Hz, 1 H), 4.72–4.76 (m, 2 H), 4.62–4.66 (m, 2 H), 2.99 (q, J = 6.8 Hz, 2 H), 1.61 (h, J = 7.3 Hz, 2 H), 0.97 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 65.3, 65.9, 104.8, 112.4, 123.7, 128.0, 131.7, 133.0, 155.7, 156.4, 159.7, 163.5, 166.3.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details on synthesis and characterization of the sulfamide and 4,6-dichloropyrimidine building blocks and the target compounds **8** and **17**–**71**. Two X-ray single crystal structures of compound **17** crystallized from different solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The corresponding data sets have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom, http://www.ccdc.cam.ac.uk/, under the following deposition numbers: 888522 (crystals from methanol), 888506 (crystals from EtOAc/hexane).

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +41 61 565 65 65. Fax: + 41 61 565 65 00. E-mail: martin.bolli@actelion.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge our co-workers Nassilia Attaba, Heiner Bammerlin, Bruno Capeleto, Stephane Delahaye, Udo Diessenbacher, Fabienne Drouet, Céline Mangold, David Monnard, Pascal Rebmann, Pauline Schrepfer, Walter Schmutz, Laure Thenoz, René Vogelsanger, Daniel Wanner, and Aude Weigel for the excellent work delivered, Prof. Dr. Henri Ramuz for scientific advice, and Dr. Markus Neuburger (University of Basel) for technical advice.

■ ABBREVIATIONS USED

ABC, area between curves; CHO, Chinese hamster ovary; CSD, Cambridge Structural Database; ELSD, evaporative light scattering detector; ET, endothelin; ET_A, endothelin A receptor; ET_B, endothelin B receptor; EtOAc, ethyl acetate; KOtBu, potassium *tert*-butoxide; MAP, mean arterial pressure; SEM, standard error of the mean

■ REFERENCES

(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Goto, K.; Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* **1988**, *332*, 411–415.

(2) Battistini, B.; Botting, R. Endothelins: A Quantum Leap Forward. *Drug News Persp.* **1995**, *8*, 365–391.

(3) Kohan, D. E. Endothelin-1 and Hypertension: From Bench to Bedside. *Curr. Hypertens. Rep.* **2008**, *10*, 65–69.

(4) Thorin, E.; Clozel, M. The Cardiovascular Physiology and Pharmacology to Endothelin-1. *Adv. Pharmacol.* **2010**, *60*, 1–26.

(5) Remuzzi, G.; Perico, N.; Benigni, A. New Therapeutics that Antagonize Endothelin: Promises and Frustrations. *Nature Rev. Drug Discovery* **2002**, *1*, 986–1001.

(6) Clozel, M.; Flores, S. Endothelin Receptors as Drug Targets in Chronic Cardiovascular Diseases: The Rationale for Dual Antagonism. *Drug Dev. Res.* **2006**, *67*, 825–834.

(7) Fonseca, C.; Abraham, D.; Renzoni, E. A. Endothelin in Pulmonary Fibrosis. *Am. J. Respir. Cell Mol. Biol.* **2011**, *44*, 1–10.

(8) Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863–2867.

(9) Webb, M. L.; Meek, T. D. Inhibitors of Endothelin. *Med. Res. Rev.* **1997**, *17*, 17–67.

(10) Iglarz, M.; Clozel, M. At the heart of tissue: endothelin system and end-organ damage. *Clin. Sci.* **2010**, *119*, 453–463.

(11) Khimji, A.-K.; Rockey, D. C. Endothelin—biology and disease. *Cell. Signalling* **2010**, *22*, 1615–1625.

(12) Clozel, M.; Gray, G. A. Are There Different ET_B Receptors Mediating Constriction and Relaxation? *J. Cardiovasc. Pharmacol.* **1995**, *26*, S262–S264.

(13) Harada, N.; Himeno, A.; Shigematsu, K.; Sumikawa, K.; Niwa, M. Endothelin-1 Binding to Endothelin Receptors in the Rat Anterior Pituitary Gland: Possible Formation of an ET_A–ET_B Receptor Heterodimer. *Cell. Mol. Neurobiol.* **2002**, *22*, 207–226.

(14) Gregan, B.; Jürgensen, J.; Papsdorf, G.; Furkert, J.; Schaefer, M.; Beyermann, M.; Rosenthal, W.; Oksche, A. Ligand-Dependent Differences in the Internalization of Endothelin A and Endothelin B Receptor Heterodimers. *J. Biol. Chem.* **2004**, *279*, 27679–27987.

(15) Sauvageau, S.; Thorin, E.; Villeneuve, L.; Dupuis, J. Change in pharmacological effect of endothelin receptor antagonists in rats with pulmonary arterial hypertension: Role of ET_B-receptor expression levels. *Pulm. Pharmacol. Ther.* **2009**, *22*, 311–317.

(16) Iglarz, M.; Clozel, M. Mechanisms of ET-1-induced Endothelial Dysfunction. *J. Cardiovasc. Pharmacol.* **2007**, *50*, 621–628.

(17) Dagassan, P. H.; Breu, V.; Clozel, M.; Künzli, A.; Vogt, P.; Turina, M.; Kiowski, W.; Clozel, J.-P. Up-Regulation of Endothelin-B Receptors in Atherosclerotic Human Coronary Arteries. *J. Cardiovasc. Pharmacol.* **1996**, *27*, 147–153.

(18) Abraham, D. J.; Vancheeswaran, R.; Dashwood, M. R.; Rajkumar, V. S.; Pantelides, P.; Shi-wen, X.; du Bois, R. M.; Black, C. M. Increased Levels of Endothelin-1 and Differential Endothelin Type A and B Receptor Expression in Scleroderma-Associated Fibrotic Lung Disease. *Am. J. Pathol.* **1997**, *151*, 831–841.

(19) Bauer, M.; Wilkens, H.; Langer, F.; Schneider, S. O.; Lausberg, H.; Schäfers, H.-J. Selective Upregulation of Endothelin B Receptor Gene Expression in Severe Pulmonary Hypertension. *Circulation* **2002**, *105*, 1034–1036.

(20) Saleh, D.; Furukawa, K.; Tsao, M.-S.; Maghazachi, A.; Corrin, B.; Yanagisawa, M.; Barnes, P. J.; Giaid, A. Elevated Expresseion of Endothelin-1 and Endothelin-converting Enzyme-1 in Idiopathic Pulmonary Fibrosis: Possible Involvement of Proinflammatory Cytokines. *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 187–193.

(21) Lehrke, I.; Waldherr, R.; Ritz, E.; Wagner, J. Renal endothelin-1 and endothelin receptor type B expression in glomerular diseases with proteinuria. *J. Am. Soc. Nephrol.* **2001**, *12*, 2321–2329.

UNITED THERAPEUTICS CORP., EX1006, page 369
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

(22) Wu-Wong, J. R.; Padley, R. Endothelin receptor antagonists: A clinical study up-date. *Curr. Opin. Cardiovasc. Pulm. Renal Invest. Drugs* **2000**, *2*, 339–344.
(23) Wu, C. Recent discovery and development of endothelin receptor antagonists. *Exp. Opin. Ther. Patent* **2000**, *10*, 1653–1668.
(24) Boss, C.; Bolli, M.; Weller, T. Endothelin Receptor Antagonists: Structures, Synthesis, Selectivity and Therapeutic Applications. *Curr. Med. Chem.* **2002**, *9*, 349–383.
(25) Iqbal, J.; Sanghi, R.; Das, S. K. Endothelin Receptor Antagonists: An Overview of Their Synthesis and Structure–Activity Relationship. *Mini-Rev. Med. Chem.* **2005**, *5*, 381–408.
(26) Aubert, J.-D.; Juillerat-Jeanneret, L. Therapeutic potential of endothelin receptor modulators: lessons from human clinical trials. *Expert Opin. Ther. Targets* **2009**, *13*, 1069–1084.
(27) Houde, M.; Labonté, J.; D'Orléans-Juste, P. Peptide and Non-peptide Antagonists Targeting Endothelin Receptors in Physiology and Pathology. *Curr. Pharm. Des.* **2011**, *17*, 2613–2625.
(28) Hoette, S.; O'Callaghan, D. S.; Jardim, C.; Souza, R. Dual receptor blockade by bosentan: clinical experience in treatment of pulmonary hypertension. *J. Recept., Ligand Channel Res.* **2010**, *3*, 113–121.
(29) Dwyer, N.; Kilpatrick, D. Bosentan for the treatment of adult pulmonary hypertension. *Future Cardiol.* **2011**, *7*, 19–37.
(30) *Tracleer*; European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000401/human_med_001100.jsp&murl=menus/ (Accessed May 2012).
(31) Blalock, S. W.; Matulevicius, S.; Mitchell, L. C.; Reimold, S.; Warner, J.; Peshock, R.; Torres, F.; Chin, K. M. Long-Term Outcomes With Ambrisentan Monotherapy in Pulmonary Arterial Hypertension. *J. Card. Failure* **2010**, *16*, 121–127.
(32) Frampton, J. E. Ambrisentan. *Am. J. Cardiovasc. Drugs* **2011**, *11*, 215–226.
(33) *Volibris*; European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000839/human_med_001151.jsp&mid=WC0b01ac058001d124 (Accessed May 2012).
(34) Goligorsky, M. S.; Iijima, K.; Morgan, M.; Yanagisawa, M.; Masaki, T.; Lin, L.; Nasjletti, A.; Kaskel, F.; Frazer, M.; Badr, K. F. Role of Endothelin in the Development of Dahl Hypertension. *J. Cardiovasc. Pharmacol.* **1991**, *17*, S484–S491.
(35) Doucet, J.; Gonzalez, W.; Baptiste, J. Endothelin Antagonists in Salt-Dependent Hypertension Associated with Renal Insufficiency. *J. Cardiovasc. Pharmacol.* **1996**, *27*, 643–651.
(36) Schiffrin, E. L. Role of endothelin-1 in hypertension and vascular disease. *Am. J. Hypertens.* **2001**, *14*, 83S–89S.
(37) Fattinger, K.; Funk, C.; Pantze, M.; Weber, C.; Reichen, J.; Stieger, B.; Meier, P. J. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: A potential mechanism for hepatic adverse reactions. *Clin. Pharmacol. Ther.* **2001**, *69*, 223–231.
(38) Neidhart, W.; Breu, V.; Burri, K.; Clozel, M.; Hirth, G.; Klinkhammer, U.; Giller, T.; Ramuz, H. Discovery of Ro 48–5695: A Potent Mixed Endothelin Receptor Antagonist Optimized from Bosentan. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2223–2228.
(39) Harrington, P. J.; Khatri, H. N.; DeHoff, B. S.; Guinn, M. R.; Boehler, M. A.; Glaser, K. A. Research and Development of a Second-Generation Process for Bosentan, an Endothelin Receptor Antagonist. *Org. Process Res. Dev.* **2002**, *6*, 120–124.
(40) Bolli, M.; Boss, C.; Fischli, W.; Clozel, M.; Weller, T. Novel Sulfamides and Their Use as Endothelin Receptor Antagonists. WO2002053557, Jul 11, 2002.
(41) Bolli, M. H.; Boss, C.; Clozel, M.; Fischli, W.; Hess, P.; Weller, T. The Use of Sulfonylamido Pyrimidines Incorporating an Unsaturated Side Chain as Endothelin Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 955–959.
(42) Boss, C.; Fischli, W.; Weller, T.; Clozel, M.; Bolli, M. Novel Sulfamides. WO2006051502, May 18, 2006.
(43) Burri, K.; Clozel, M.; Fischli, W.; Hirth, G.; Löffler, B. M.; Ramuz, H. Verwendung von Sulfonamiden als Heilmittel und neue Sulfonamide. EP0510526, Oct 28, 1992.
(44) Burri, K.; Clozel, M.; Fischli, W.; Hirth, G.; Löffler, B.-M.; Ramuz, H.; Neidhart, W. Sulfonamide, ihre Herstellung und Verwendung als Heilmittel und Zwischenprodukte. EP0526708, Feb 10, 1993.
(45) Yamada, K.; Yasuda, K.; Kikkawa, K.; Kohno, R. Sulfonamide derivative and process for preparing the same. EP0743307, Nov 20, 1996.
(46) Yamada, K.; Yasuda, K.; Kikkawa, K.; Kohno, R. Sulfonamide Derivate und Verfahren zu deren Herstellung. EP0959072, Oct 31, 2002.
(47) Bolli, M.; Boss, C.; Clozel, M.; Fischli, W.; Weller, T. Pyrimidine-Sulfamides and Their Use as Endothelin Receptor Antagonist. WO2004050640, Jun 17, 2004.
(48) Brown, D. J.; Lyall, J. M. Pyrimidine Reactions. *Aust. J. Chem.* **1964**, *17*, 794–802.
(49) Crosby, D. G.; Berthold, R. V. *n*-Butyl 5-Chloro-2-pyrimidoxyacetate—A Plant Growth Regulator Analog. *J. Org. Chem.* **1960**, *25*, 1916–1919.
(50) Maggiali, C.; Morini, G.; Mossini, F.; Morini, G.; Barocelli, E. H1-antihistaminic and antimuscarinic effects of 2- and 4-[benzyl-(2-dimethylaminoethyl)amino]pyrimidine compounds. *Farmaco, Ed. Sci.* **1988**, *43*, 277–292.
(51) Wacker, D. A.; Rossi, K. A.; Wang, Y. Preparation of pyridones as GPR119 G protein-coupled receptor agonists. WO2009012275, Jan 22, 2009.
(52) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T.; Gupton, J. T. Preparation of novel β-trifluoromethyl vinamidinium salt and its synthetic application to trifluoromethylated heterocycles. *Tetrahedron Lett.* **1996**, *37*, 1829–1832.
(53) Morimoto, H.; Ohashi, N.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Potent and Selective ET-A Antagonists. 2. Discovery and Evaluation of Potent Water Soluble *N*-(6-(2-Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives. *J. Med. Chem.* **2001**, *44*, 3369–3377.
(54) Clozel, M.; Breu, V.; Burri, K.; Cassal, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. *Nature* **1993**, *365*, 759–761.
(55) Neidhart, W.; Breu, V.; Bur, D.; Burri, K.; Clozel, M.; Hirth, G.; Müller, M.; Wessel, H. P.; Ramuz, H. The Discovery of Nonpeptide Endothelin Receptor Antagonists. Progression towards Bosentan. *Chimia* **1996**, *50*, 519–524.
(56) Breu, V.; Burri, K.; Cassal, J.-M.; Clozel, M.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. Novel Sulfonamides. WO9619459, Jun 27, 1996.
(57) Morimoto, H.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Potent and Selective ET-A Antagonists. 1. Synthesis and Structure–Activity Relationship of *N*-(6-(2-Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives. *J. Med. Chem.* **2001**, *44*, 3355–3368.
(58) Morimoto, H.; Shimadzu, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Modifications and Structure–Activity Relationships at the 2-Position of 4-Sulfonamido-pyrimidine Derivatives as Potent Endothelin Antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 81–84.
(59) Brockway, B. P.; Mills, P. A.; Azar, S. H. A New Method for Continuous Chronic Measurement and Recording of Blood Pressure, Heart Rate and Activity in the Rat via Radio-Telemetry. *Clin. Exp. Hypertens.—Theory Pract* **1991**, *A13*, 885–895.
(60) Guiol, C.; Ledoussal, C.; Surgé, J.-M. A Radiotelemetry System for Chronic Measurement of Blood Pressure and Heart Rate in the Unrestrained Rat Validation of the Method. *J. Pharmcol. Toxicol. Methods* **1992**, *28*, 99–105.
(61) Hess, P.; Clozel, M.; Clozel, J.-P. Telemetry monitoring of pulmonary arterial pressure in freely moving rats. *J. Appl. Physiol.* **1996**, *81*, 1027–1032.

UNITED THERAPEUTICS CORP., EX1006, page 370
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

(62) Iglarz, M.; Binkert, C.; Morrison, K.; Fischli, W.; Gatfield, J.; Treiber, A.; Weller, T.; Bolli, M. H.; Boss, C.; Buchmann, S.; Capeleto, B.; Hess, P.; Qiu, C.; Clozel, M. Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **2008**, *327*, 736−745.
(63) Sidharta, P. N.; van Giersbergen, P. L. M.; Halabi, A.; Dingemanse, J. Macitentan: entry-into-humans study with a new endothelin receptor antagonist. *Eur. J. Clin. Pharmacol.* **2011**, *67*, 977−984.
(64) Gabbay, E.; Fraser, J.; McNeil, K. Review of bosentan in the management of pulmonary arterial hypertension. *Vasc. Health Risk Manage.* **2007**, *3*, 887−900.
(65) Dhillon, S.; Keating, G. M. Bosentan—A Review of its Use in the Management of Mildly Symptomatic Pulmonary Arterial Hypertension. *Am. J. Cardiovasc. Drugs* **2009**, *9*, 331−350.
(66) Dhillon, S. Bosentan—A Review of its Use in the Management of Digital Ulcers Associated with Systemic Sclerosis. *Drugs* **2009**, *69*, 2005−2024.
(67) *Study of ACT-064992 on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT00660179 (Accessed May 2012).
(68) *Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-1)*; ClinicalTrials.gov,, http://clinicaltrials.gov/ct2/show/NCT01474109 (Accessed May 2012).
(69) *Macitentan for the Treatment of Digital Ulcers in System Sclerosis Patients (DUAL-2)*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT01474122 (Accessed May 2012).
(70) *Macitentan in Combo With Dose-dense Temozolomide in Patients With Recurrent Glioblastoma*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT01499251 (Accessed May 2012).
(71) Zhong, Z.; Bibbs, J. A.; Yuan, W.; Wong, C.-H. Active-Site-Directed Modification of Subtilisin. *J. Am. Chem. Soc.* **1991**, *113*, 2259−2263.

UNITED THERAPEUTICS CORP., EX1006, page 371
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Brittany La/Stephanie Owusu-Hemeng
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $200 paid	1252	1	400	400

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**400**

Electronic Acknowledgement Receipt	
EFS ID:	17191300
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La/Stephanie Owusu-Hemeng
Filer Authorized By:	Brittany La
Attorney Docket Number:	AC-66-USC
Receipt Date:	22-OCT-2013
Filing Date:	05-SEP-2012
Time Stamp:	12:17:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$400
RAM confirmation Number	11836
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Miscellaneous Incoming Letter	AC-66-USC_Miscellaneous_Communication.pdf	19349 584bc7be2761e23f648afe5b48f48e933d21173c	no	1
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	EXHIBIT_B.pdf	629374 c80f77f289b4c102e367dbd6d2f32e7b935f34c9	no	14
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30150 d942ee9dbc290feac7fc4afe404f528b0fecbee0	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	678873	

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 11/27/2013
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
11/27/2013	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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/604,148	CLOZEL, MARTINE	
	SREENI PADMANABHAN	Art Unit 1627	

Document Code - AP.PRE.DEC

Notice of Panel Decision from Pre-Appeal Brief Review

This is in response to the Pre-Appeal Brief Request for Review filed 10/22/2013.

1. ☐ **Improper Request** – The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☒ **Proceed to Board of Patent Appeals and Interferences** – A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☒ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: *1-14*.
Claim(s) withdrawn from consideration: _____.

3. ☐ **Allowable application** – A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☐ **Reopen Prosecution** – A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) */SREENI PADMANABHAN/*.
(2) *Larry Helms*.
(3) *Kendra Carter*.
(4)_____.

UNITED THERAPEUTICS CORP., EX1006, page 377
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Applicant:	Martine CLOZEL	)	Examiner:	CARTER, Kendra D.
		)		
Serial No.:	13/604,148	)	Group Art Unit:	1627
		)		
Filed:	September 5, 2012	)	Confirmation No.:	5499
		)		
Title:	THERAPEUTIC COMPOSITIONS	)	Docket: AC-66-USC	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

This Appeal Brief is being submitted pursuant to the Notice of Appeal filed on October 21, 2013, in response to the Final Office Action mailed June 20, 2013 ("Final Office Action"). Because a Pre-Appeal Brief Request for Review was also filed on October 21, 2013 and the Notice of Panel Decision from Pre-Appeal Brief Review ("the Pre-Appeal Decision") was issued on November 27, 2013, advising to proceed to Board of Patent Appeals and Interferences, the Pre-Appeal Decision resets the time period for filing an appeal brief to one-month from the mailing of the Decision or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. As this Appeal Brief is filed within one-month from the mailing of the Pre-Appeal Decision (November 27, 2013), it is believed no fees are due. If any additional fees are required or if the enclosed payment is insufficient, Appellant requests that the required fees be charged to Deposit Account No. 50-4255.

For the reasons stated herein, Appellant respectfully request reversals of the final rejection and obviousness-type double patenting rejection and remand for allowance of the pending claims.

I. REAL PARTY IN INTEREST

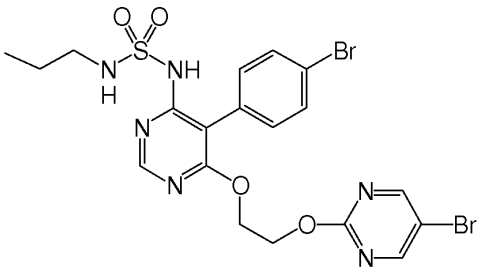
The real party in interest in this appeal is Actelion Pharmaceuticals Ltd. by virtue of an assignment submitted in this application. The assignment was recorded on September 5, 2012, at Reel 028901, Frame 0418.

II. RELATED APPEALS, INTEREFERENCES, AND OTHER PROCEEDINGS

To the best of Appellant's knowledge, there exist no appeals, interferences, or other proceedings that are related to this application.

III. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 1-14 are pending and stand rejected. Independent claim 1 is directed to 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):

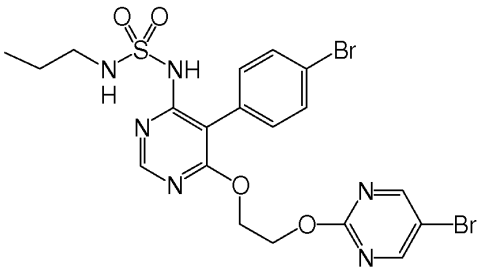


(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

Independent claim 12 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

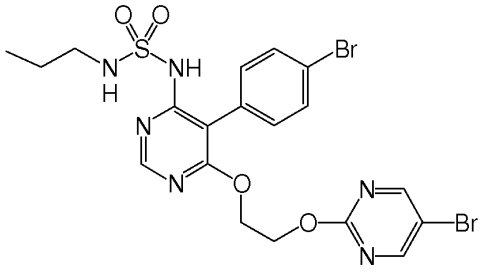
UNITED THERAPEUTICS CORP., EX1006, page 379
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

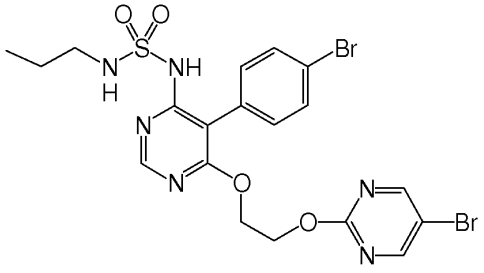
Independent claim 13 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

Independent claim 14 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

UNITED THERAPEUTICS CORP., EX1006, page 380
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

IV. ARGUMENT

Claims 1-14 are pending. The Examiner rejected claims 1-14 under 35 U.S.C. § 103 for being obvious over International Pub. No. WO 2002/053557 to Bolli et al., ("Bolli") in view of International Pub. No. WO 2006/026395 to Keyser et al. ("Keyser"). The Examiner also rejected claims 1-14 on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") and claims 1-11 of U.S. Patent No. 8,268,847 ("the '847 Patent") in view of Bolli and Keyser. The Examiner further provisionally rejected claims 1-14 on the ground of nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142 ("the '142 application") in view of Bolli and Keyser. Appellant respectfully requests reversal of the Examiner's finding for failing to apply the legal standard adopted by the Federal Circuit for analyzing obviousness under 35 U.S.C. §103 and obviousness-type double patenting.

A. Rejection under 35 U.S.C. § 103(a)

Independent claim 1 of the present application is directed to a method for 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 PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form. Independent claims 12, 13 and 14 are directed to methods of treating pulmonary arterial hypertension comprising administering simultaneously, over a period of time and separately, 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 of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form, respectively. The Examiner rejected claims 1-14 under 35 U.S.C. § 103 for being obvious over Bolli in view of Keyser.

The Examiner noted that Bolli teaches the instant compound of formula (I) on page 28 of the reference. Although Bolli does not teach a combination of the compound of formula (I) with a PDE5 inhibitor, the Examiner argued that the combination is obvious because Keyser teaches

UNITED THERAPEUTICS CORP., EX1006, page 381
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

that ET_A antagonists and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat hypertension, pulmonary hypertension and pulmonary arterial hypertension. Keyser discloses a number of ET_A antagonists in paragraphs [062], [063] and in Table 1. Keyser does not disclose the compound of formula (I) of the present claims. Appellant respectfully disagrees.

There is no motivation to select the instant compound of Formula (I) from page 28 of Bolli to combine with PDE5 inhibitor of Keyser because said compound of formula (I) is not the lead compound and is not taught to be ET_A selective.

The Federal Circuit has specifically held that the framework for analysis as to the obviousness of chemical formulations involves a "lead-modification" analysis similar to that involving novel compounds. *Unigene Laboratories, Inc. et al. v. Apotex, Inc., et al.,* 655 F.3d 1352, 1361-1362 (Fed. Cir. 2011), applying the analytical framework of *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.,* 492 F.3d 1350, 1356 (Fed. Cir. 2007) and its progeny. First, a lead or reference formulation is identified from the art, and then a flexible teaching-suggestion-motivation (TSM) test is applied to determine whether there is reason or motivation to modify the lead formulation to make the claimed invention with a reasonable expectation of success. *Id. See also, Ex parte Subramanyam, et al.,* B.P.A.I. Decision January 15, 2010, Appeal No. 2009-012300 pp. 7-8; *Ex parte Subramanyam*, B.P.A.I. Decision March 29, 2010, Appeal No. 2010-002463. *Unigene* elaborates on the well-established principle that neither general disclosures nor mere identification in the prior art of each component of a composition can establish that the combination as a whole would have been obvious. *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (emphasis added). As the Supreme Court held in *KSR*, "it will be necessary . . . to determine whether there was an apparent reason to combine [or modify] the known elements [in the prior art] in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." *KSR Int'l., Co. v. Teleflex, Inc*., 127 S. Ct. 1727, 1740 – 1741 (2007).

Here, the Examiner argued that it would have been obvious to select the second compound on page 28 of Bolli to combine with a PDE5 inhibitor as taught by Keyser. Even though no ET_A and ET_B data are disclosed for the compound on page 28 of Bolli, the Examiner argued that Keyser defines selective ET_A antagonist useful for their invention to display a relative receptor binding ratio of at least 100. As such, according to the Examiner, one skilled in the art

UNITED THERAPEUTICS CORP., EX1006, page 382
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

would be motivated to choose any of the compounds of Bolli that have greater selectivity for ET_A over ET_B with reasonable expectation of success and motivation that the combination with PDE5 inhibitor would provide treatment for hypertension and pulmonary hypertension. The Examiner further argued that because the compound on page 28 is structurally similar to Example 104 of Bolli, which has an activity ratio of about 683, the compound on page 28 of Bolli is therefore expected to have similar activity and therefore, is encompassed by Keyser.

The Examiner is effectively arguing that because Keyser teaches a broad genus (here ET_A antagonist), all species that fall under that genus (here, all compounds that fall under Keyser's definition of ET_A) would be obvious. This argument, however, has been rejected by the Federal Circuit. *See In re Baird*, 16 F.3d 380, 382, (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). Therefore, identification of a genus does not render the species *prima facie* obvious. If the analysis were to start with Keyser, one skilled in the art would not select Example 104 from Bolli as a lead compound out of the universe of ET_A compounds (which extends beyond the Bolli reference) because Keyser does not point to Bolli. It is further noted that sitaxsentan, which is disclosed in the lead formuation of Keyser, has a high specificity for ET_A, being 6,500-fold more selective as an antagonist for ET_A compared to ET_B (see Keyser, p. 15, ¶ [058]). Therefore, one skilled in the art would not select Example 104, which has a much lower selectivity ratio of about 683 to replace sitaxsentan. If the analysis were to start with Bolli, the "most preferred" compounds are identified on page 23. There is no motivation to select Example 104 as the lead compound.

Even if Example 104 were chosen as the lead, there is no motivation to modify the lead compound to arrive at the compound of formula (I) claimed herein.

Even if one skilled in the art were to choose Example 104 as the lead, which Appellant continues to contest, there is no motivation to then move on to the analogs disclosed on pages 24-28 of Bolli where ET_A/ET_B activities are not disclosed, and choose, without any guidance, the second compound disclosed on page 28 as the compound of choice to replace sitaxsentan in Keyser. The Examiner argued that one skilled in the art would expect the activity ratio of the compound on page 28 to be similar to the N-ethyl analog of Example 104, which ET_A:ET_B selectivity ratio is disclosed in Bolli. Appellant respectfully disagrees. Biological activities are generally unpredictable and cannot be extrapolated in the abstract as the Examiner did. Even if

UNITED THERAPEUTICS CORP., EX1006, page 383
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

biological activities can be extrapolated, there are 16 other compounds disclosed on pages 24-28, which are structural similar to Example 104. Nothing specifically points to the second compound on page 28 as the preferred compound. Selecting the compound of Appellant's claims from Bolli would require choosing it from among the over 200 Bolli examples, without the benefit of any ET_A and ET_B inhibition data, despite the presence in Bolli of 134 compounds that did have ET_A-ET_B binding data. Clearly, such a selection could only be made using impermissible hindsight, with Appellant's disclosure as a guide.

Alternatively, one could also very well choose as a lead compound, Example 24 of Bolli which has comparable or even better selectivity against ET_A than Example 104. In that instant, the skilled artisan would then also have to consider the first six compounds on page 26 and the first four compounds on page 27 as possibilities as, according to the Examiner's logic, they are expected to have similar activities to Example 24. With so many possibilities and no particular guidance, there is again no reason to select the second compound on page 28 of Bolli as the compound of choice. With other possible lead compounds and an infinite number of modifications that could be made to these leads, there clearly is no finite number of predictable solutions to the problem here. The Federal Circuit in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs, Inc.* 520 F.3d 1358, 1365 (Fed. Cir. 2008) specifically rejected an analysis which starts off with "simply retrac[ing] the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention [ ] was obvious" as similarly done by the Examiner here in this case. The Federal Circuit specifically requires "a flexible TSM test[, which] remains the primary guarantor against a non-statutory hindsight analysis".

Keyser specifically teaches away from using a compound having non-selective ET activity, particularly compounds having ET_B antagonistic activity.

Keyser teaches that "use of 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". P. 19, ¶ [067]. Keyser explicitly excludes Bosentan because it works by blocking both ET_A and ET_B. P. 19-20, ¶ [068]. Keyser explains the opposite effect of ET_A and ET_B as follows:

> . . . ET_A causes vasoconstriction, while ET_B causes vasodilation . . . Bosentan works by blocking both ET_A and ET_B receptors. Sitaxsentan works by only

UNITED THERAPEUTICS CORP., EX1006, page 384
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

> 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 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.

Id. (emphasis added). Thus, the use of an ET_A-selective antagonist (with little or no antagonistic activity on ET_B) is a fundamental aspect of the Keyser teaching. In reading this in combination with Bolli, one skilled in the art would not be motivated to select a compound having ET_B activity as the lead compound as there would be no expectation of success. As such, one skilled in the art would not be motivated to choose the compound of Example 104, which as ET_B activity, as the lead compound. One skilled in the art also would not select the second compound on page 28 of Bolli to be combined with Keyser because if one presumes activity to be similar to Example 104, the combination would not be an ideal choice. Accordingly, Appellant respectfully asserts that the Examiner can only select Example 104 as the lead compound and identify motivation to modify to the compound on page 28 of Bolli using hindsight of the current invention. The Examiner has not established a legally sufficient motivation to select the currently claimed compound to be used in combination with the teaching of Keyser. In the absence of such legally sufficient motivation, the present rejection cannot be maintained, and should be withdrawn.

The present invention is also not obvious because it produces an unexpected effect.

According to p. 19-20, ¶ [067] and [068] of Keyser, a compound which has ET_B antagonistic activity is expected to interfere with vasodilation and therefore is expected to be less effective in combination with a PDE5 inhibitor (discussed above).

The claimed compound of formula (I), now known as Macitentan, has an *in vitro* ET_A:ET_B antagonistic activity of about 1:782 as can be calculated from the information provided in a later-published reference Iglarz et al., *Journal of Pharmacology and Experimental Therapeutics*, Vol. 329, No. 3 (2008) ("Iglarz"), previously submitted in an Information

UNITED THERAPEUTICS CORP., EX1006, page 385
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Disclosure Statement. This compound, however, is confirmed to exhibit dual ET_A/ET_B antagonistic activity. For instance, Iglarz shows in Table 4 on page 740 that in a functional assay, the selectivity of ET_A/ET_B is only 50:1. Significantly, in an *in vivo* study, the author states:

> **In Vivo Pharmacology Studies.** Macitentan is best studied in vivo because this allows the study of the overall pharmacological effects of macitentan together with its metabolite. When administered to normotensive rats, **macitentan, like bosentan, increased plasma ET-1 concentration, confirming its dual blockade on both ET_A and ET_B receptors**. This increase occurred at a 10-fold lower dose than with bosentan, indicating a more potent pharmacological activity in vivo (Fig. 2). (emphasis added)

Thus, Macitentan (or the compound of formula (I) of the current invention), like Bosentan, is considered by those skilled in the art to be a dual ET_A-ET_B receptor antagonist. As also confirmed by a later-published article by Bolli et al., *J. Med. Chem.* (2012) 55:7849-7861 (submitted herewith as Exhibit B), Macitentan was selected not only because of the increased potency on the ET_A receptor, but because it also blocks the ET_B receptor in vivo. *Id.* at p. 7850 and 7855. Given the explicit disclosure in Keyser of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A-ET_B receptor antagonists such as Bosentan, one skilled in the art would not have any expectation of success in the use of Macitentan, a dual ET_A/ET_B antagonist, in combination with a PDE5 inhibitor.

Contrary to Keyser, Appellant has surprisingly found that the combination of the compound of formula (I), i.e., Macitentan, with a compound having PDE5-inhibitory properties results in an unexpected effect in the treatment of diseases wherein vasoconstriction is involved. The results, shown in the specification in Examples 1-3, are summarized in the Table below:

Example	Model	PDE5 Inhibitor	ABC for PDE5 Inhibitor	ABC for Macitentan	ABC for PDE5 Inhibitor + Macitentan
1	Dahl salt-sensitive rat Model	Tadalafil	310	256	923
2	Spontaneously 25	Tadalafil	286	44	444

UNITED THERAPEUTICS CORP., EX1006, page 386
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

	hypertensive rat model				
3	Spontaneously 25 hypertensive rat model	Sildenafil	229	38	317

It can be seen that in all three Examples, the combination of the PDE5 inhibitor and the compound of Formula I (or Macitentan) provided ABC values that were unexpected; i.e., greater than the sum of the ABC values for administration of either component alone.

The Examiner argued that there is no evidence that the claimed compound is unexpected to be better than the N-ethyl analog taught by Bolli. Appellant notes that neither Bolli nor Keyser discloses any unexpected results of the N-ethyl analog in combination with a PDE5 inhibitor. Keyser simply teaches the use of an ET_A-selective antagonist in combination with a PDE5 inhibitor for the treatment of cardiac disorders such as PAH. Example 1 of Keyser simply shows that sildenafil does not appear to impact sitaxsentan pharmacokinetics while no data is shown for the efficacy study in Example 2. Therefore, Keyser does not show any unexpected result at all.

The Examiner failed to consider the unexpected results provided in the application. In view of the preceding remarks, Appellant respectfully asserts that claims 1-11 are not obvious in view of the combination of Bolli and Keyser, particularly claims 12-14 where data provided in the specification supports the unobviousness of the combination. Appellant respectfully requests withdrawal of this rejection.

B. Double Patenting Rejections

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") in view of Bolli and Keyser. Claims 1-14 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142 ("the '142 application") in view of Bolli and Keyser. Appellant notes that the '142 application has now issued as U.S. Patent No. 8,367,685. The Office Action appears to base its rejection on the same rationale as the instant rejection under 35 U.S.C. § 103 for alleged obviousness over Bolli in view of Keyser. However, as discussed in detail above, there is no motivation to combine the compound claimed in the '142 application (now the '685 patent) or the '781 patent with a PDE5 inhibitor as Keyser teaches away from this combination. Contrary to Keyser's teaching, the combination claimed possesses unexpected results as there is no reduced efficacy, but in fact enhanced efficacy

UNITED THERAPEUTICS CORP., EX1006, page 387
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

seen in administering the claimed combination (discussed above). In view of the foregoing remarks, Appellant respectfully requests withdrawal of the rejection under obviousness-type double patenting.

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of the parent case, U.S. Patent No. 8,268,847 ("the '847 patent") in view of Bolli and Keyser. The present application is a continuation of the application leading to the '847 patent. Appellant will consider filing a terminal disclaimer over the '847 patent upon an indication of otherwise allowable subject matter in the present application.

FOR THESE REASONS, Appellant respectfully petitions this Honorable Board to reverse the Examiner's rejection of the pending claims for obviousness and obviousness-type double patenting.

To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 50-4255.

Respectfully Submitted,

Date: December 27, 2013

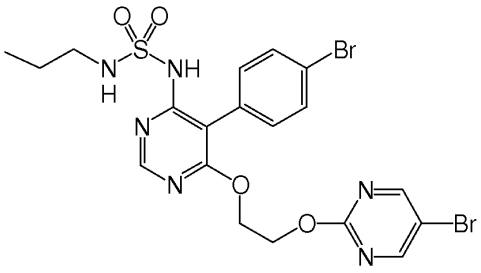
By: */Brittany La/*

Brittany La
Reg. No. 58,337
Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
(973) 912-5232

UNITED THERAPEUTICS CORP., EX1006, page 388
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

CLAIMS APPENDIX

1. (Previously Presented) 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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. (Previously Presented) The method according to claim 0, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. (Previously Presented) The method according to claim 0, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. (Previously Presented) The method according to claim 0, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. (Previously Presented) The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

UNITED THERAPEUTICS CORP., EX1006, page 389
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

6. (Previously Presented) The method according to claim 5, wherein said administration will not exceed one day.

7. (Previously Presented) The method according to claim 0, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

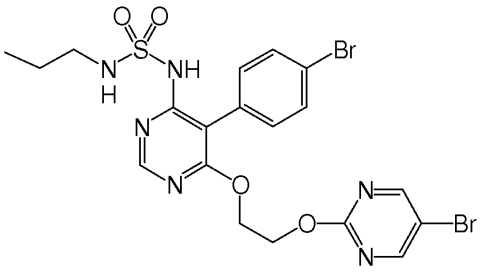
8. (Previously Presented) The method according to claim 0, wherein the compound having PDE5-inhibitory properties is sildenafil.

9. (Previously Presented) The method according to claim 0, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. (Previously Presented) The method according to claim 0, wherein the disease intended to be treated is pulmonary hypertension.

11. (Previously Presented) The method according to claim 0, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

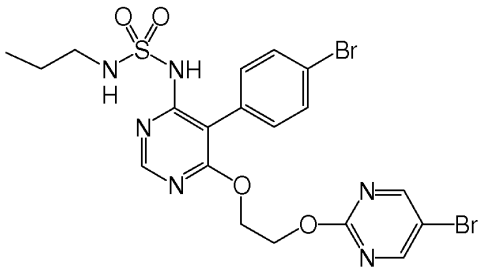


(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

13. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

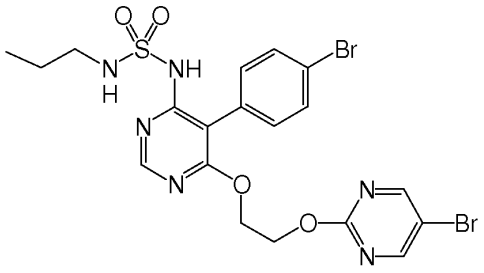
UNITED THERAPEUTICS CORP., EX1006, page 390
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 391
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

EXHIBIT B

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

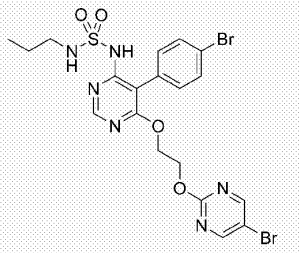
The Discovery of *N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-*N*′-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist

Martin H. Bolli,* Christoph Boss, Christoph Binkert, Stephan Buchmann, Daniel Bur, Patrick Hess, Marc Iglarz, Solange Meyer, Josiane Rein, Markus Rey, Alexander Treiber, Martine Clozel, Walter Fischli, and Thomas Weller

Drug Discovery Chemistry, Actelion Pharmaceuticals Ltd., Gewerbestrasse 16, CH-4123 Allschwil, Switzerland

Supporting Information

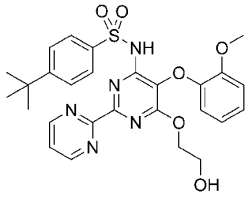
ABSTRACT: Starting from the structure of bosentan (**1**), we embarked on a medicinal chemistry program aiming at the identification of novel potent dual endothelin receptor antagonists with high oral efficacy. This led to the discovery of a novel series of alkyl sulfamide substituted pyrimidines. Among these, compound **17** (macitentan, ACT-064992) emerged as particularly interesting as it is a potent inhibitor of ET_A with significant affinity for the ET_B receptor and shows excellent pharmacokinetic properties and high in vivo efficacy in hypertensive Dahl salt-sensitive rats. Compound **17** successfully completed a long-term phase III clinical trial for pulmonary arterial hypertension.



INTRODUCTION

Over the past decade, our understanding of the function of endothelin (ET) has evolved from describing it as a purely vascular factor regulating blood pressure[1−4] to recognizing it as a hormone influencing many cellular processes such as proliferation, apoptosis, and migration leading to tissue hypertrophy, remodeling, fibrosis, and inflammation.[5−7] The three structurally closely related peptides, named endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin-3 (ET-3), are among the most potent vasoconstrictors known in humans. They convey their action through binding to two G-protein coupled receptors called ET_A and ET_B. Among the three isopeptides, ET-1 appears to be the key player in the cardiovascular system. ET-2 and ET-3 are specifically expressed in the gastrointestinal tract and the brain, respectively.[8,9] On the vascular side, ET_A receptors are mainly expressed on smooth muscle cells, mediating vasoconstriction, while ET_B receptors expressed on endothelial cells and smooth muscle cells cause vasodilation and vasoconstriction, respectively. In addition, a wealth of tissue cells such as cardiomyocytes, renal cortex, and medulla cells, fibroblasts, macrophages, and neurons produce ET-1 and/or express the two ET receptors, illustrating that the ET system is not confined to the vasculature only.[9−11] Cross talk and receptor heterodimer formation has been proposed for the two ET receptors.[6,12−15] Both ET_A and ET_B receptors are involved in mediating ET-1 deleterious effects in diseases such as chronic heart failure, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, or kidney disease.[6,7,10,16] Furthermore, in many pathological situations, the ET system is up-regulated and a change in the ET_A/ET_B expression ratio in favor of ET_B is observed in diseased tissue.[11,17−19] Several studies corroborate that increased activity of the ET system in tissue correlates with disease severity.[20,21]

A large number of synthetic endothelin receptor antagonists have been investigated preclinically, and several small molecule inhibitors have been studied in clinical trials for chronic heart failure, hypertension, cancer, and fibrosis.[5,22−27] Today, the dual ET_A/ET_B receptor antagonist bosentan (**1**, Figure 1)[28−30] and the ET_A selective antagonist (*S*)-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoic acid (ambrisentan)[31−33] are approved treatments for pulmonary arterial hypertension.



1 (Bosentan)
IC_{50} ET_A 45 nM
ET_B 202 nM

Figure 1. Structure and in vitro activity of compound **1**. IC_{50} values as measured with a ^{125}I-ET-1 binding assay.

Received: June 28, 2012
Published: August 3, 2012

ACS Publications © 2012 American Chemical Society

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 393
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

When we initiated our medicinal chemistry program to identify a follow-up compound to sulfonamide **1** (Figure 1), we decided that compound **1** should not only serve as the structural starting point for our quest for novel endothelin antagonists but should also represent the benchmark against which we gauge our novel compounds. A candidate suitable for clinical development needs to meet the following requirements: (1) The compound has to show a significantly increased potency on the ET_A receptor when compared to compound **1**. (2) The compound should block the ET_B receptor in vivo. (3) The compound needs to demonstrate oral efficacy superior to the one of compound **1** as assessed by measuring arterial blood pressure in conscious hypertensive Dahl salt-sensitive rats.[34−36] (4) Pharmacokinetic properties assessed in animals must support once daily dosing in humans. (5) The compound should easily distribute into tissue in order to also reach ET receptors expressed in the tissue. (6) Because compound **1** inhibits the canalicular bile salt export pump,[37] a candidate compound must be devoid of bile salt transport inhibition.

In the paragraphs below, we describe our efforts aimed at identifying a compound that meets all of the above criteria.

RESULTS AND DISCUSSION

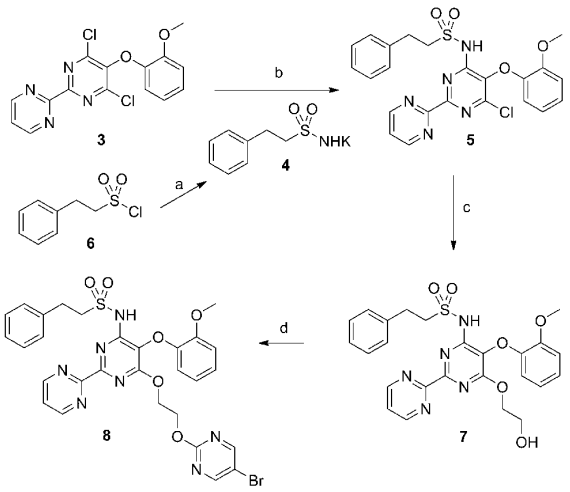
Synthesis. The following description of the synthesis of a prototypical sulfonamide (Scheme 1) and sulfamide (Scheme 2 and 3) endothelin receptor antagonist shall illustrate the general approach chosen to prepare the compounds discussed in this manuscript.

The preparation of the sulfonamide derivatives was carried out as previously described[38−42] and usually started by reacting a dichloro-pyrimidine building block[43,44] (e.g., **3**) with a sulfonamide potassium salt (e.g., **4**) in DMSO at room temperature to give the monochloro-pyrimidine intermediate (e.g., **5**). The sulfonamide potassium salts were readily accessible by treating the respective sulfonyl chloride (e.g., **6**) with ammonia, followed by potassium *tert*-butylate in methanol, while the necessary dichloro-pyrimidines were obtained as described in the literature.[40,42−46] The monochlorides such as **5** were treated with a freshly prepared solution of sodium in ethylene glycol at elevated temperatures to give the corresponding alcohols (e.g., **7**). The alcohols were dissolved in THF and deprotonated with 2.5 equiv of sodium hydride and reacted with the respective 2-chloro- or 2-(methylsulfonyl) pyrimidines at elevated temperature. As reported earlier,[47] these pyrimidines are either commercially available or prepared according to literature procedures.[48−52] Final products such as **8** were obtained in good yields as white to beige powders after crystallization from methanol.

The preparation of the various sulfamide building blocks needed for the synthesis of our sulfamide based endothelin receptor antagonists is exemplified with the propyl-sulfamide potassium salt **13** shown in Scheme 2.[40] The procedure starts by reacting chlorosulfonyl isocyanate (**9**) dissolved in dichloromethane at 0 °C with 1 equiv of *tert*-butanol to give the BOC-protected amino-sulfonyl-chloride (**10**), which was subsequently added slowly to a solution of 1 equiv of the respective amine (e.g., *n*-propylamine) in the presence of 3 equiv of triethylamine in dichloromethane at 0 °C. The mixture was stirred overnight to drive the reaction to completion and was then concentrated. The residue was dissolved in a large volume of ethyl acetate. To avoid extraction of the BOC-protected sulfamides such as **11** into water, reagents and salts were removed by washing the ethyl acetate solution very carefully with a small volume of water and brine only. The organic extract was dried, and the sulfamide **11** was isolated by evaporating the solvent. This material was dissolved in approximately 5 M HCl in dioxane to affect BOC-deprotection. After stirring the mixture at room temperature for 4−8 h, the solvent was evaporated to give sulfamide **12**. The potassium salt **13** was obtained by dissolving **12** in methanol followed by the addition of potassium *tert*-butylate and subsequent evaporation of the solvent. Purification of the potassium salt **13** was achieved by trituration in diethylether and drying under high vacuum. Overall yields of the above process were good to excellent.

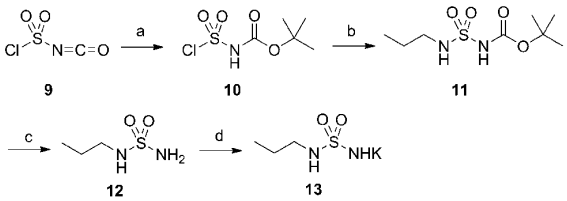
Synthesis of the sulfamide based endothelin receptor antagonists followed the preparation of the corresponding sulfonamide analogues. As an example, the preparation of sulfamide **17** is outlined in Scheme 3. Hence, reacting a dichloro-pyrimidine building block (e.g., **14**[42]) with a sulfamide

Scheme 1. General Synthesis of Sulfonamide Endothelin Receptor Antagonists Exemplified with 8[a]



[a]Reagents and conditions: (a) (i) **6**, NH_3 in MeOH, rt, 16 h, (ii) MeOH, KOtBu, rt 3 h, 83−89% over 2 steps; (b) **3**, DMSO, rt, then **4**, rt, 16 h, 89%; (c) ethylene glycol, Na, 2 h, then **5**, 70−90 °C, 18 h, 73−91%; (d) **7**, THF, NaH, 1 h, then 2-chloro-5-bromopyrimidine, 75 °C, 2 h, 43%.

Scheme 2. Synthesis of Sulfamide Potassium Salt Building Blocks[a]

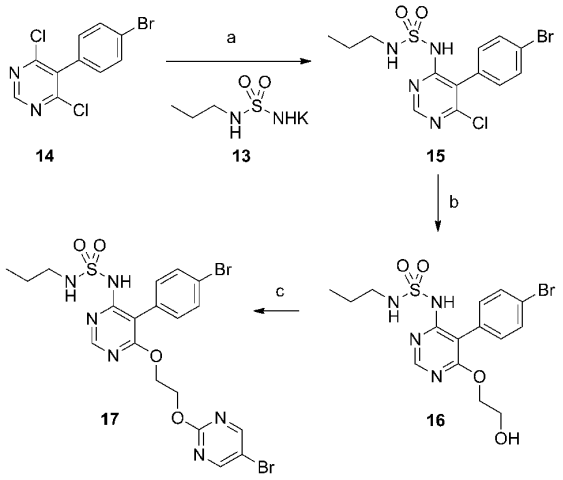


[a]Reagents and conditions: (a) *tert*-BuOH, DCM, 0 °C to rt, 1 h; (b) add mixture prepared in (a) to propylamine, NEt_3, DCM, 0 °C then 16 h rt; (c) 5 M HCl in dioxane, rt, 4−8 h; (d) MeOH, KOtBu, rt, 3 h, 46−98% over 4 steps.

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 394
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Scheme 3. General Synthesis of Sulfamide Endothelin Receptor Antagonists Exemplified with 17[a]



[a]Reagents and conditions: (a) **14**, DMSO, rt, **13**, rt, 24–72 h, 83–93% (b) ethylene glycol, DME, KOtBu, 10 min, then **15**, 100 °C, 18–24h, 86–89%; (c) **16**, THF, NaH, 0.5–1 h, then 2-chloro-5-bromopyrimidine, 60–75 °C, 2 h, 88%.

potassium salt such as **13** in DMSO at room temperature for 24–48 h gave the monochloro-pyrimidine intermediates (e.g., **15**). The ethylene-glycol side chain was introduced by applying similar conditions as described for the synthesis of the sulfonamides. Alternatively, the monochloride (e.g., **15**) was added to a mixture of 3 equiv of potassium *tert*-butylate and about 40 equiv of ethylene glycol in dimethoxyethane. These mixtures were usually heated to 90–100 °C for 24–70 h to furnish the corresponding alcohols (e.g., **16**) in yields of 70–90%. The final step, the attachment of the substituted pyrimidine, was performed as described for the sulfonamide derivatives in Scheme 1. For the preparation of compound **17**, 2-chloro-5-bromo-pyrimidine was used. In general, the target compounds could be purified easily by recrystallization from methanol.

In Vitro SAR Discussion. Inspired by the structure of Tanabe's clinical development compound *N*-(6-(2-((5-bromopyrimidin-2-yl)oxy)ethoxy)-5-(*p*-tolyl)pyrimidin-4-yl)-4-(1-hydroxy-2-methylpropan-2-yl)benzenesulfonamide (T-0201, **2**)[53] (Figure 2), we were curious to learn how the introduction of a pyrimidine to the ethylene glycol moiety of compound **1** would

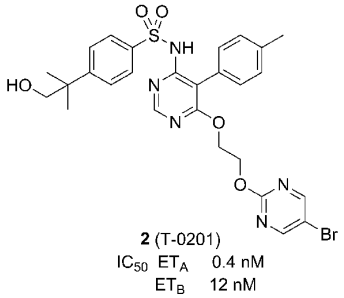
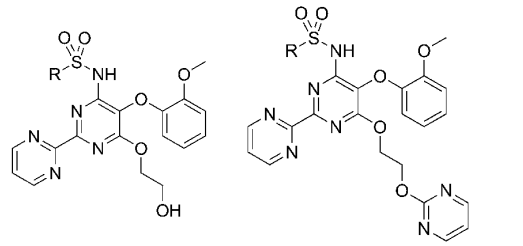


Figure 2. Structure and in vitro activity of compound **2**. IC_{50} values as measured with a ^{125}I-ET-1 binding assay.

influence its affinity for the two endothelin receptors. In a first study illustrated by the compounds listed in Table 1, we

Table 1. Effect of Additional Pyrimidine at Ethylene Glycol[a]



R	compd	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]	compd	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
4-*tert*-butyl phenyl	**1**	45.0	202	**18**	4.3	76
phenethyl	**19**	25.7	1131	**20**	8.0	465
methyl	**21**	4534	9506	**22**	739	1765

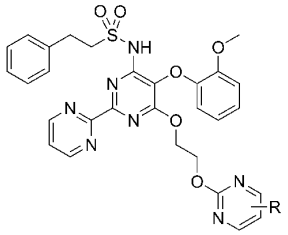
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

observed that such an additional pyrimidine ring improves the affinity for ET_A and ET_B significantly. Compound **1** derivative **18**, for instance, is about 10 times more potent on ET_A and about three times more active on ET_B than compound **1** itself. A similar trend was observed with the pair of phenylethane sulfonamides **19** and **20**. Interestingly, also the weakly active methane sulfonamide derivative **21** profits from the introduction of a pyrimidine ring, and the resulting compound **22** is almost 10 times more potent on both ET_A and ET_B than compound **21**. We therefore had a closer look at the structure–activity relationship (SAR) of this additional pyrimidine moiety. While various substituents were tolerated in the 5-position of the pyrimidine, substituents in positions 4 and/or 6 clearly hampered the compound's affinity for the ET receptors. This is illustrated with some examples of the phenylethane sulfonamide series compiled in Table 2. A comparable SAR, however, was observed with other scaffolds. Compared to the unsubstituted pyrimidine derivative **20**, the 5-methyl analogue **23** is less potent on both receptors. On the other hand, a 5-chloro (**24**), 5-bromo (**8**), 5-methoxy (**25**), 5-methylthio (**26**), and a 5-trifluoromethyl (**27**) substituent all led to a similarly improved affinity for ET_A. While the bromo-, methoxy-, and trifluoromethyl substituent improved the potency on ET_B only slightly, a 5-methylthio group increased the compound's affinity for this receptor significantly. The 5-cyclopropyl substitutent in **28** reproduced the profile of its unsubstituted analogue **20**. As illustrated with compound **29**, a 4,6-disubstitution pattern yielded only poorly active compounds.

On the one hand attaching a 5-bromo or a 5-methylthio-pyrimidine to the ethylene glycol moiety brought us closer to our goal of identifying endothelin antagonists more potent than compound **1**. On the other hand, these new compounds contain five aromatic rings and have a molecular weight well above 600 g/mol and therefore certainly do not qualify as lean molecules. In view of this, we carefully scrutinized the three substituents attached to positions 2, 4, and 5 of the core pyrimidine for possibilities to reduce the molecule's size. For these studies, we kept the 5-bromo-pyrimidine residue at the

UNITED THERAPEUTICS CORP., EX1006, page 395
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

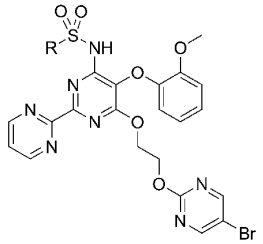
Table 2. Optimization of Pyrimidine[a]



compd	R	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
20	hydrogen	8.0	465
23	5-methyl	17.8	1501
24	5-chloro	2.8	461
8	5-bromo	2.2	216
25	5-methoxy	3.2	202
26	5-methylthio	1.1	42
27	5-trifluoromethyl	3.0	145
28	5-cyclopropyl	7.7	424
29	4,6-dimethoxy	4775	>10000

[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

Table 3. From Sulfonamides to Sulfamides[a]



compd	R	IC_{50} ET_A [nM]	IC_{50} ET_B [nM]
30	4-*tert*-butyl phenyl	1.5	19.3
31	phenyl	10.4	341
32	benzyl	73	3479
8	phenethyl	2.2	216
33	3-phenyl-propyl	6.7	377
34	methyl	113	1146
35	ethyl	14	460
36	*n*-propyl	9.4	566
37	*n*-butyl	4.3	552
38	benzyl-NH−	1.9	147
39	methyl-NH−	7.9	194
40	ethyl-NH−	9.9	655
41	*n*-propyl-NH−	3.8	322
42	*n*-butyl-NH−	1.7	167
43	*N*-benzyl-methyl-N-	7.0	457
44	morpholino	187	1474

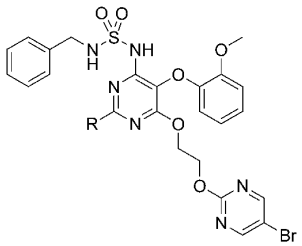
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. Note that compounds **8** and **30**−**37** represent sulfonamides, while compounds **38**−**44** represent sulfamides.

ethylene glycol constant. The compounds listed in Table 3 document the SAR of the sulfonamide part in position 4. Tables 4 and 5 illustrate the influence of the substituents in position 2 and 5, respectively.

In a first step, we removed the *tert*-butyl group attached to the benzene sulfonamide moiety. This resulted in a 10-fold loss of affinity for both ET receptors. When a CH_2 group was introduced as linker between the phenyl ring and the sulfur to give compound **32**, a further loss of affinity was observed. Interestingly, moving the phenyl two CH_2 units away from the sulfonamide moiety (compound **8**) restored the compound's affinity completely for the ET_A receptor and partially for the ET_B receptor. The affinity profile of phenyl-propane sulfonamide **33** is very similar to the one of the ethane analogue **32**. These observations combined with our aim to reduce molecular weight prompted us to study compounds lacking a phenyl ring in the sulfonamide part. Not unexpectedly though, the methane sulfonamide derivative **34** showed only moderate potency on the ET_A receptor. Much to our delight, however, the ethane sulfonamide **35** was almost as potent as the much bulkier phenylethane sulfonamide **8**. As shown with compounds **36** and **37**, the affinity for ET_A improves steadily with increasing length of the alkyl chain. No such trend was observed with the ET_B receptor. In a next step, we prepared a number of compounds wherein the sulfonamide moiety was replaced by a sulfamide group. As illustrated with compounds **38**−**43**, these novel sulfamide derivatives represent potent ET receptor antagonists. Only the morpholine derivative **44** shows some loss of affinity toward the two receptors. Compared to the corresponding sulfonamides, the sulfamides have almost identical affinity for the ET_A receptor (e.g., compare **8** with **38**, **35** with **39**, **36** with **40**, **37** with **41**). In contrast to the sulfonamide series, however, the IC_{50} value for the ET_B receptor improves with increasing length of the sulfamide alkyl chain. More importantly, the sulfamides show a trend toward improved potency on ET_B. This observation clearly moved the sulfamides into the focus of our interest. For the following studies, we selected sulfamide **38** as a reference compound. Hence, while keeping the benzyl sulfamide moiety constant, we prepared a series of analogues with different substituents in position 2 of the core pyrimidine. Several examples are compiled in Table 4. The pyrazine (**45**) and morpholine (**47**) derivatives showed an affinity profile almost identical to the one of the pyrimidine analogue **38**. The pyridine derivative **46**, on the other hand, lost potency, in particular on the ET_B receptor. As illustrated with compounds **48** and **49**, the loss in affinity is clearly more pronounced for the 2-cyclopropyl (**48**) and the 2-methoxy (**49**) substituted pyrimidine scaffolds. The 2-methoxy−ethoxy substituent in compound **50** led to a small loss in affinity for both receptors when compared to **38**. Interestingly, complete removal of the substituent in position 2 of the core pyrimidine (**51**) reproduced the affinity profile of compound **50**, suggesting that the contribution of the 2-substituent to the binding affinity is small. This encouraged us to further evaluate the sulfamide series with scaffolds lacking a substituent in position 2 of the core pyrimidine. We therefore prepared a number of 2-unsubstituted pyrimidine derivatives incorporating a selection of 5-substituents that were known to lead to potent ET receptor antagonists.[53−58] Some examples are compiled in Table 5. As shown with compounds **52** and **53**, a 3-methoxyphenoxy rather than a 2-methoxyphenoxy substituent led to an increase in potency on ET_A but left the affinity for ET_B unchanged. An unsubstituted phenyl ring directly bound to the core pyrimidine as in **54** had no impact on ET_A affinity

UNITED THERAPEUTICS CORP., EX1006, page 396
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 4. Optimization of Scaffold: 2-Substituent



compd	R	IC_{50} ET_A[a] [nM]	IC_{50} ET_B[a] [nM]
38	2-pyrimidinyl	1.9	147
45	2-pyrazinyl	2.1	166
46	4-pyridyl	3.4	561
47	4-morpholinyl	1.4	192
48	cyclopropyl	14	1082
49	methoxy	40	2490
50	2-methoxy-ethoxy	6.9	554
51	hydrogen	6.9	525

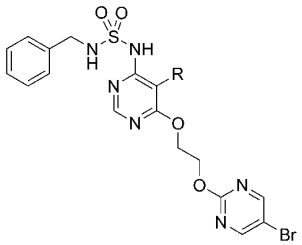
[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements.

but caused a significant loss in the activity on ET_B. Introducing a methyl group (**55**), or a chlorine (**56**) or bromine (**57**) atom to the para position of the phenyl ring improved the compounds' affinity for both receptors significantly. Introducing even larger alkyl groups, as shown with compounds **58** and **59**, did not improve the compound's affinity any further. In fact, both compounds showed a clearly reduced potential to block the ET_B receptor.

In brief, the SAR studies discussed so far have shown that: (1) Introduction of a 5-bromo- or 5-methylthiopyrimidine to the ethylene glycol improves the compound's affinity for both ET receptors significantly (Table 1 and 2). (2) The bulky 4-*tert*-butyl benzene sulfonamide in compound **1** can be replaced by a benzyl or alkyl sulfamide moiety (Table 3). (3) Sulfamide derivatives are more potent on ET_B when compared to the corresponding sulfonamide analogues (Table 3). (4) A 2-substituent at the core pyrimidine is not mandatory to obtain potent ET antagonists (Table 4). (5) A 3-methoxyphenoxy, 4-methylphenyl, 4-chlorophenyl, or 4-bromophenyl residue attached to position 5 of the core pyrimidine leads to potent ET receptor antagonists (Table 5).

In Vivo Efficacy Assessment. In a next step, we assessed in vivo the oral efficacy of some of the most potent examples listed in Table 5. For this purpose, we measured the blood pressure lowering effect following oral administration by gavage of 3 mg/kg of each compound in conscious hypertensive Dahl salt-sensitive rats equipped with telemetry.[59−61] In this model, efficient blockade of the ET receptors results in a significant reduction of mean arterial blood pressure.[35] The pharmacological response was quantified by calculating the area between the curves (ABC) of the blood pressure recordings 24 h before and after treatment. As this experiment allowed for rapid and reliable assessment of the in vivo efficacy, we did not measure pharmacokinetic properties prior to pharmacological testing. In all experiments, the heart rate remained unaffected (data not shown). At an oral dose of 3 mg/kg, compound **1** maximally reduced mean arterial blood pressure by −7 ± 4 mmHg. The duration of action was about 15 h, which translated into an ABC of −88 mmHg·h (n = 8) (Table 5). A maximal reduction of mean arterial blood pressure by −30 ± 3 mmHg was achieved with a dose of 100 mg/kg. At this dose, compound **1** was active for about 72 h and displayed an ABC of −896 mmHg·h (n = 5).

Table 5. Optimization of Scaffold: 5-Substituent



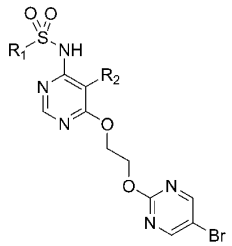
compd	R	IC_{50} ET_A[a] [nM][a]	IC_{50} ET_B[a] [nM][a]	max ΔMAP[b] [mmHg]	ABC[c] [mm Hg·h] (n)
1	*d*	45	202	−7 ± 4	−88 (8)
52	3-methoxyphenoxy	1.0	457	−10 ± 4	−245 (5)
53	2-chloro-5-methoxyphenoxy	1.4	712	−24 ± 5	−639 (5)
54	phenyl	6.8	5067	nd	nd
55	4-methylphenyl	0.7	441	nd	nd
56	4-chlorophenyl	1.4	506	−18 ± 6	−593 (6)
57	4-bromophenyl	1.6	461	−14 ± 3	−445 (6)
58	4-ethylphenyl	2.3	1264	nd	nd
59	4-isopropyl-phenyl	3.6	2474	nd	nd

[a]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. [b]Maximal mean arterial blood pressure reduction as extracted from the moving average over 6 h. [c]Area between curve (ABC) as calculated from the blood pressure recordings 24 h before and after administration of 3 mg/kg of the compound to conscious hypertensive Dahl salt-sensitive rats, max. ΔMAP = maximal reduction in mean arterial blood pressure; n = number of animals in the experiment, nd = not determined. [d]For the structure of compound **1**, see Figure 1.

dx.doi.org/10.1021/jm3009103 | *J. Med. Chem.* 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 397
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 6. Optimization of the Sulfamide Moiety[a]



compd	R_1	R_2	IC_{50} ET_A[b] [nM]	IC_{50} ET_B[b] [nM]	max ΔMAP[c] [mmHg]	ABC[d] [mm Hg·h] (*n*)
57	benzyl-NH−	4-bromophenyl	1.6	461	−14 ± 3	−445 (6)
60	methyl-NH−	4-bromophenyl	1.7	812	−21 ± 6	−1045 (5)
61	ethyl-NH−	4-bromophenyl	0.8	830	−20 ± 10	−598 (6)
17	*n*-propyl-NH−	4-bromophenyl	0.5	391	−25 ± 6	−922 (6)
62	*n*-butyl-NH−	4-bromophenyl	0.3	158	−16 ± 4	−443 (5)
63	cyclopropyl-NH−	4-bromophenyl	4.4	1474	nd	nd
64	*N*-benzyl-methyl-N−	4-bromophenyl	4.3	5208	nd	nd
65	morpholino	4-bromophenyl	2.8	2829	nd	nd
66	*n*-propyl-NH−	4-chlorophenyl	1.2	784	nd	nd
67	*n*-propyl-NH−	3-methoxyphenoxy	1.9	468	−15 ± 3	−391 (6)
68	*n*-propyl-NH−	6-chloro-3-methoxyphenoxy	0.4	208	−21 ± 5	−500 (6)
69	*n*-propyl	4-bromophenyl	2.2	3058	−25 ± 4	−1116 (6)
70	*n*-butyl	4-bromophenyl	1.1	2424	−22 ± 3	−734 (5)

[a]Note that compounds **17**, **57**, and **60**−**68** represent sulfamides, while compounds **69** and **70** are sulfonamides. [b]IC_{50} values as determined in binding assays using membranes of Chinese hamster ovary (CHO) cells containing either the recombinant ET_A or ET_B receptor, respectively. Data are given as geometric means of at least three independent measurements. [c]Maximal mean arterial blood pressure reduction as extracted from the moving average over 6 h. [d]Area between curve (ABC) as calculated from the blood pressure recordings 24 h before and after administration of 3 mg/kg of the compound to conscious hypertensive Dahl salt-sensitive rats; max ΔMAP = maximal reduction in mean arterial blood pressure; *n* = number of animals in the experiment; nd = not determined.

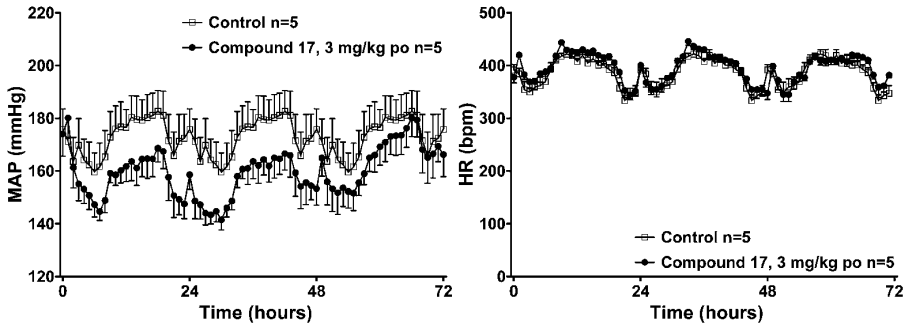


Figure 3. Mean arterial blood pressure (MAP, left) and heart rate (HR, right) recordings in conscious hypertensive Dahl salt-sensitive rats before (control) and after oral administration of 3 mg/kg of compound **17**. Results are expressed as mean ± SEM.

As apparent from the in vivo data given in Table 5, compounds incorporating a 3-methoxyphenoxy (**52**), 2-chloro-5-methoxyphenoxy (**53**), a 4-chlorophenyl (**56**), or a 4-bromophenyl (**57**) substituent at position 5 of the core pyrimidine clearly exceeded the in vivo activity of compound **1**. At this point, we decided to evaluate sulfamides with a 4-bromophenyl substituted pyrimidine scaffold in more detail. Several examples prepared for this study are listed in Table 6. For the ET_A receptor, the 4-bromophenyl derivatives reproduce the relative SAR observed with the corresponding 2-methoxyphenoxy analogues (Table 3) on a higher potency level (e.g., **39** vs **60**, **40** vs **61**, **44** vs **65**), and several compounds reach affinities below 1 nM. With respect to ET_B, the relative SAR between the 4-bromophenyl derivatives and the 2-methoxyphenoxy-analogues is again similar. However, this time the bromo-phenyl derivatives in Table 6 are often less potent when compared to their analogues in Table 3 (e.g., **38** vs **57**, **43** vs **64**). Notable exceptions are compounds **17** and **62**, which both retain their ET_B affinity.

When we tested the sulfamides of Table 6 in our rat model of hypertension, compounds incorporating a rather small alkyl sulfamide showed excellent in vivo activity (e.g., **60**, **61**, **17**). The propyl-sulfamide **17** emerged as a particularly interesting compound as it combined high in vivo efficacy with high potency on ET_B. We therefore extended our study to the three propyl sulfamides incorporating a 4-chlorophenyl (**66**), a 3-methoxyphenoxy (**67**), or a 6-chloro-3-methoxyphenoxy (**68**) substituent in position 5 of the core pyrimidine (Table 6). The in vitro activity of compound **66** was inferior to the one of compound **17** as it was clearly less potent on ET_B. While the 3-

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 398
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

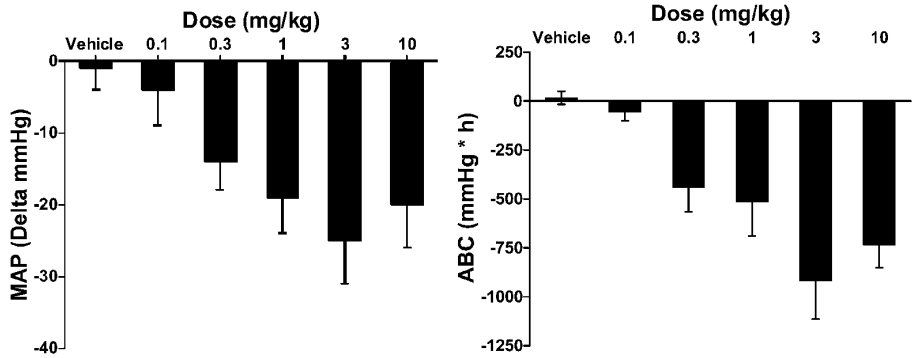


Figure 4. Dose–response curve of mean arterial blood pressure (MAP) reduction and area between curves (ABC) in hypertensive Dahl salt-sensitive rats after oral administration of compound **17** in 5% arabic gum. Results are expressed as mean ± SEM.

methoxyphenoxy derivative **67** was only slightly less potent than **17**, the chloro substituted analogue **68** was more potent on ET_B. However, both compounds **67** and **68** showed a clearly lower activity in vivo. A comparison of sulfamide **17** with sulfonamides **69** and **70** confirmed our earlier finding that the sulfamides present a significantly higher affinity for the ET_B receptor. In our context, the sulfonamides **69** and **70** are therefore clearly less attractive despite their high in vivo activity in the Dahl salt-sensitive rat model of hypertension (Table 6).

In brief, the *n*-propylsulfamide derivative **17**, later named macitentan,[62] fulfilled the requirements we set forth at the beginning of our discovery program. Sulfamide **17** is highly potent on the ET_A receptor with significant affinity for the ET_B receptor and maximally reduces mean arterial blood pressure for at least 60 h at an oral dose of 3 mg/kg (Figure 3). Following a dose–response experiment, maximal reduction of mean arterial blood pressure by −25 ± 6 mmHg was reached with a dose of 3 mg/kg (Figure 4). No change in heart rate was observed over the range of 1–100 mg/kg in conscious Dahl salt-sensitive rats (Figure 3, data not shown). In a multiple dose experiment, Dahl salt-sensitive rats were treated for five consecutive days with 1 mg/kg/day of **17** (Figure 5). Mean arterial blood pressure was stably reduced by −20 mmHg over the whole treatment period and returned to baseline about 48 h after the last dose was given. No signs of tachyphylaxis were observed, and no rebound effect manifested at the end of the study as blood pressure values returned to baseline.

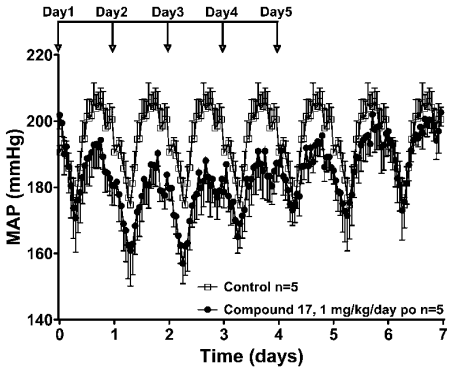


Figure 5. Mean arterial blood pressure (MAP) recordings of a repeated dose experiment administering 1 mg/kg/day of compound **17** over five consecutive days to hypertensive Dahl salt-sensitive rats equipped with telemetry (ABC = 1842 mmHg·h). Results are expressed as mean ± SEM.

In view of the excellent pharmacodynamic behavior of compound **17**, it came as no surprise that **17** also showed favorable pharmacokinetic properties (Table 7). In an iv experiment with male Wistar rats, the compound showed a low plasma clearance of 6.7 mL/min·kg translating into a half-life of 5.1 h. The volume of distribution reached 1.8 L/kg, indicating that the compound is distributing well into tissues. At an oral dose of 10 mg/kg, compound **17** reached a peak plasma concentration of 1670 ng/mL at 6 h after administration. Oral bioavailability was 69%. A similar pharmacokinetic behavior was found in the dog, emphasizing the compound's attractiveness for further development. In the dog, compound **17** was rapidly (T_{max} = 2 h) and almost completely (F = 87%) absorbed and reached plasma concentrations close to 5000 ng/mL after oral administration of 10 mg/kg. Clearance and half-life are comparable in rat and dog.

In the course of our PK studies we discovered that compound **17** is metabolized to the depropylated sulfamide **71** (Figure 6). This compound represents a major metabolite reaching plasma exposure levels 4–5 times higher than that of **17**. Sulfamide **71** binds to the ET_A and ET_B receptors with IC_{50} values of 3.4 and 987 nM, respectively and therefore clearly adds to the pharmacological activity of the parent compound **17**.[62] As we learned later, metabolite **71** is also formed in humans.[63] Interestingly, oral administration of 10 mg/kg of the butyl analogue **62** to Wistar rats also led to significant plasma concentrations (C_{max} = 4100 ng/mL at 6 h after administration) of sulfamide **71**.

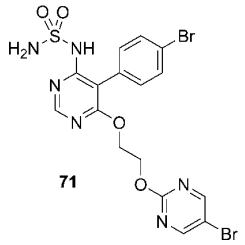
In 10.9% of the patients treated with compound **1**, a transient, dose dependent increase in serum liver aminotransferase levels of >3 times the upper limit of normal is observed.[64−66] Mechanistically, this observation has been attributed to the ability of compound **1** to inhibit bile salt transport in hepatocytes, eventually leading to intrahepatic cholestasis.[37] Minimizing the interaction of a potential follow-up compound with hepatic bile acid transport has therefore been a further goal of our optimization efforts. Several compounds have been assessed for their potential to interact with bile salt transport in a rat model,[37] and compound **17** showed no sign of bile salt transport inhibition in this model (data not shown).

UNITED THERAPEUTICS CORP., EX1006, page 399
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Table 7. PK Parameters of 17 in Male Wistar Rats and Male Beagle Dogs

species	iv dose[a] [mg/kg]	AUC_{0-inf} [ng h/mL]	CL [mL/min·kg]	Vss [L/kg]	$t_{1/2}$ [h]	oral dose[b] [mg/kg]	AUC_{0-inf} [ng h/mL]	C_{max} [ng/mL]	T_{max} [h]	F [%]
Wistar rat (n = 5)	1	2680 ± 730	6.7 ± 2.1	1.8 ± 0.9	5.1 ± 1.9	10	18500 ± 8100	1670 ± 371	6.0	69
beagle dog (n = 3)	1	3170 ± 520	5.4 ± 1.0	0.9 ± 0.2	4.1 ± 0.4	10	27500 ± 6500	4590 ± 2540	2.0	87

[a]Wistar rat: solution in 50 mM aqueous tris(hydroxymethyl)methylamine (Tris) pH 8.3 buffer containing 45% PEG400; beagle dog: solution in 25% *N*-methylpyrrolidone (NMP), 25% PEG400, 50% 50 mM aqueous Tris pH 8.3 buffer. [b]Wistar rat: suspension in 7.5% aqueous modified gelatin; beagle dog: solution in PEG400.



71

Figure 6. Stucture of sulfamide **71**, a major metabolite of compound **17** in Wistar rats and Beagle dogs.

CONCLUSIONS

In conclusion, starting from the structure of compound **1**, we have discovered a novel series of highly potent ET receptor antagonists. While these novel compounds are still based on a pyrimidine core, the *tert*-butyl benzene sulfonamide part of compound **1** has been replaced by a series of simple alkyl sulfamide moieties. When compared to the corresponding sulfonamides, these novel sulfamides are characterized by an enhanced affinity for the ET_B receptor, rendering them a particularly interesting class of novel ET receptor antagonists. In addition, many of these sulfamides show high oral efficacy in reducing arterial blood pressure in conscious hypertensive Dahl salt-sensitive rats. In vivo dealkylation of the alkyl sulfamide moiety in compounds **17** and **62**, for instance, to the pharmacologically active sulfamide **71** is another interesting feature of the sulfamide class as it leads to sustained pharmacological activity.

Sulfamide **17** emerged as a highly attractive candidate for further studies and can be characterized as a potent ET_A receptor antagonist with significant affinity for the ET_B receptor. In rat and dog models, the compound is well absorbed, distributes well into tissue, and is slowly cleared, suggesting that it is suitable for once daily dosing in humans. Recently published data on a phase I clinical trial with compound **17** confirm these expectations.[63] In hypertensive Dahl salt-sensitive rats, **17** efficiently and dose dependently reduced the arterial blood pressure. More detailed studies with sulfamide **17** on its tissue penetration and ability to block the ET_A and ET_B receptor in vivo have been described in a separate publication.[62] In a rat model, compound **17** did not increase plasma bile salt concentrations. Compound **17** successfully completed a phase III clinical trial for pulmonary arterial hypertension recently.[67] A phase IIIb clinical trial for digital ulcers[68,69] and a phase I/Ib trial for recurrent glioblastoma[70] are currently ongoing.

EXPERIMENTAL SECTION

Chemistry. All reagents and solvents were used as purchased from commercial sources (Sigma-Aldrich Switzerland, Lancaster Synthesis GmbH, Germany, Acros Organics USA). Moisture sensitive reactions were carried out under an argon atmosphere. Progress of the reactions was followed either by thin-layer chromatography (TLC) analysis (Merck, 0.2 mm silica gel 60 F_{254} on glass plates) or by LC-MS. LC-MS: UltiMate 3000 RS pump, UltiMate 3000 column compartment (40 °C), UltiMate 3000 RS DAD, MSQplus (all Dionex, Switzerland), Sedex 85 ELSD (Sedere, VWR Germany). Column: Zorbax SB-AQ, 5 μm, 120 Å, 4.6 mm × 50 mm (Agilent). Gradient: 5−95% acetonitrile in water containing 0.04% of trifluoroacetic acid, within 1 min. Flow: 4.5 mL/min. Or LC-MS*: Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT. Colum: Gromsil ODS4, 3 μm, 120 Å; 2 mm × 30 mm. Gradient: 0−100% acetonitrile in water containing 0.05% formic acid, within 6 min. Flow: 0.45 mL/min; t_R is given in min. Purity of the target compounds was confirmed on two additional columns: on a Waters Atlantis T3, 5 μm, 4.6 mm × 30 mm, eluting with a gradient of 5−95% of acetonitrile in water containing 0.04% of trifluoroacetic acid; and on a Waters XBridge C18, OBD, 5 μm, 4.6 mm × 50 mm (Waters, Switzerland), eluting with a gradient of 5−95% of acetonitrile in water containing 13 mM of NH_3. According to these three LC-MS analyses, all compounds showed a purity >95% (UV at 230 nm), and about 80% of the compounds showed a purity >98%. Purity and identity was further confirmed by NMR spectroscopy. HR-LC-MS: analytical pump, Waters Acquity Binary, Solvent Manager. MS: SYNAPT G2MS, source temperature 150 °C, desolvatation temperature 400 °C, desolvatation gas flow 400 L/h. Cone gas flow: 10 L/h. Extraction cone: 4 RF. lens: 0.1 V. Sampling cone: 30. Capillary: 1.5 kV. High resolution mode. Gain: 1.0. MS function: 0.2 s per scan, 120−1000 amu in full scan, centroid mode. Lock spray: leucine enkephalin 2 ng/mL (556.2771 Da) scan time 0.2 s with interval of 10 s and average of five scans. DAD: Acquity UPLC PDA detector. Column: Acquity UPLC BEH C18 1.7 μm 2.1 mm × 50 mm from Waters, thermostatted in the Acquity UPLC column manager at 60 °C. Eluents: water + 0.05% formic acid; B, acetonitrile + 0.05% formic acid. Gradient: 2−98% B over 3.0 min. Flow: 0.6 mL/min. Detection: UV 214 nm and MS, t_R is given in min. Prep HPLC: Waters XBridge Prep C18, 5 μm, OBD, 19 mm × 50 mm, gradient of acetonitrile in water containing 0.4% of formic acid, flow 75 mL/min. Melting points were determined by differential scanning calorimetry (DSC) using a DSC822e/400 instrument and the HSS7 sensor from Mettler Toledo, Switzerland. The sample is weighed in a 40 μL aluminum crucible which is open under a flow of 15 mL/min of nitrogen during the experiment. The scan goes from 20 to 320 °C at a rate of 5 K/min. The peak temperature of the melting endotherm was determined with the STARe software and was assigned to the melting point (mp). NMR spectroscopy: NMR spectra were recorded on a Varian Mercury 300VX spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) or Bruker Avance II, 400 MHz UltraShield, ^{1}H (400 MHz), ^{13}C (100 MHz); chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), h (hextet), hept (heptuplet) or m (multiplet). X-ray diffraction: Crystals of **17** were mounted on a Bruker Nonius diffractometer equipped with a CCD detector and reflections were measured using monochromatic Mo Kα radiation. The structure was solved by direct methods using SIR92, refinement was performed with CRYSTALS. Full matrix least-squares refinement was performed with anisotropic temperature factors for all atoms except hydrogen which were included at calculated positions with isotropic temperature factors. Coordinates,

UNITED THERAPEUTICS CORP., EX1006, page 400
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

anisotropic temperature factors, bond lengths, and angles will be deposited with the Cambridge Crystallographic Data Centre.

Endothelin Receptor Inhibition. Binding assays were performed in 96-well plates with CHO membranes containing the recombinant ET_A or ET_B receptors in 200 μL of 50 mM Tris-HCl, 25 mM $MnCl_2$, 1 mM EDTA pH 7.4, 0.5% BSA, 2.5% DMSO. The wells containing 0.5 μg/well of ET_A membranes or 0.2 μg/well of ET_B membranes were incubated for 2 h at RT with 15 pM [^{125}I]ET-1 (10000 cpm) in the presence or absence of test substances. Minimum and maximum binding was derived from samples with and without 1 μM of unlabeled ET-1, respectively. After the 2 h incubation period, the membranes were filtered through GF/C filterplates (MultiScreen MAHFC 1H60 from Millipore), which had been pre-equilibrated with binding buffer, using cold 50 mM Tris HCl, 0.1% BSA pH 7.5. After drying of the filterplates, 25 μL of scintillation cocktail (MicroScint 20, Perkin-Elmer) were added to each well and the filterplates were counted in a microplate counter (TopCount, Canberra Packard S.A. Zürich, Switzerland). IC_{50} values were calculated as the concentration of antagonist inhibiting 50% of the specific binding of ET-1. Two reference compounds were tested: BQ-123, a specific ET_A antagonist, and sarafotoxin 6c (Bachem, Switzerland), a specific ET_B antagonist. For these reference inhibitors, the following IC_{50} values were found (geometric mean values): ET_A mb, 20.5 nM (n = 13) for BQ-123 and >100 nM (n = 10) for Sarafotoxin; ET_B mb, 0.208 nM (n = 12) for Sarafotoxin and >1000 nM (n = 12) for BQ-123.

Telemetric in Vivo Studies.[59−61] In vivo efficacy of the compounds was assessed by oral administration of 3 mg/kg of the compound suspended in 5% arabic gum to female hypertensive Dahl salt-sensitive rats equipped with a telemetric system recording the arterial blood pressure and heart rate. For both of these parameters, each rat served as its own control by using the data of the last 24 h before treatment. An area between curve (ABC) was calculated between the control and the treatment period to assess the compound's efficacy. Maximal mean arterial blood pressure reduction was extracted from the moving average over 6 h of the blood pressure recordings.

Pharmacokinetics in the Rat. The pharmacokinetic profile was determined in the male Wistar rat (n = 5). For this purpose, compound **17** was formulated as a solution in 50 mM aqueous tris(hydroxymethyl)methylamine (Tris) pH 8.3 buffer containing 45% PEG400 for intravenous administration at a dose of 1.0 mg/kg, and as a microsuspension in 7.5% aqueous modified gelatin for oral dosing at 10 mg/kg. Blood samples were taken at regular time intervals over a period of 24 h from a preimplanted catheter, and plasma was generated by centrifugation at 4000 rpm at 4 °C. Plasma concentrations were determined using a specific and sensitive LC-MS/MS method with a limit of quantification of 1.5 ng/mL.

Pharmacokinetics in the Dog. The pharmacokinetic profile of compound **17** was determined in male beagle dogs (n = 3). The compound was administered orally at a dose of 10 mg/kg as a solution in PEG400 and intravenously at a dose of 1 mg/kg as a solution in 25% *N*-methylpyrrolidone (NMP), 25% PEG400, 50% 50 mM aqueous Tris pH 8.3 buffer.

Potassium (Phenethylsulfonyl)amide (4).[71] To a vigorously stirred solution of *N*-chlorosuccinimide (38.6 g, 289 mmol) in dichloromethane (300 mL) and water (150 mL), 2-phenyl-ethyl-mercaptane (10.0 g, 72.3 mmol) was added. The mixture became slightly warm (30 °C). The resulting suspension was stirred at rt for 3 h. The solvent was decanted, and the remaining slurry was extracted twice with dichloromethane (2 × 200 mL). The organic extracts were washed twice with satd aq $NaHCO_3$ solution and water, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was suspended in heptane:ethyl acetate 10:1, filtered, and washed with additional ethyl acetate/hexane. The filtrate was concentrated, and the crude product was purified by colum chromatography on silica gel eluting with heptane:ethyl acetate 10:1 to give 2-phenyl-ethane sulfonylchloride (8.25 g, 56%) as a pale-beige oil; R_f (silica gel, heptane:ethyl acetate 10:1) 0.32. This material (8.25 g, 40.3 mmol) was dissolved in THF (50 mL), and a solution of satd aq NH_3 (10 mL) was slowly added at −20 °C. The mixture was stirred at rt for 16 h before it was neutralized with 25% aq HCl. The organic solvent was evaporated, and the remaining residue was diluted with water (100 mL) and extracted four times with ethyl acetate (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 2-phenyl-ethane sulfonamide (6.21 g, 83%) as a pale-yellow solid. LC-MS: t_R = 0.58 min, $[M + H]^+$ = not detectable. To a solution of this material (6.21 g, 33.5 mmol) in methanol (60 mL), potassium *tert*-butylate (3.76 g, 33.5 mmol) was added. The mixture was stirred until a clear solution formed. The mixture was concentrated and the remaining residue was triturated with diethyl ether, filtered, and dried to give **4** (6.67 g, 89%) as a white powder. ^{1}H NMR (DMSO-d_6): δ 7.18−7.32 (m, 5 H), 3.05−3.11 (m, 2 H), 2.93−2.99 (m, 2 H). ^{13}C NMR (DMSO-d_6): δ 140.1, 129.0, 128.8, 126.7, 56.8, 30.9.

4,6-Dichloro-5-(2-methoxyphenoxy)-2,2′-bipyrimidine (3). Prepared as described in the literature.[39,41] LC-MS: t_R = 0.79 min, $[M + H]^+$ = 349.04. ^{1}H NMR ($CDCl_3$): δ 9.05 (d, J = 4.9 Hz, 2 H), 7.47 (t, J = 4.9 Hz, 1 H), 7.13 (td, J_t = 8.0 Hz, J_d = 1.5 Hz, 1 H), 7.00 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1 H), 6.90 (td, J_t = 8.0 Hz, J_d = 1.4 Hz, 1 H), 6.79 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 160.2, 158.2, 156.6, 155.5, 149.3, 145.0, 144.6, 125.0, 121.8, 121.0, 116.9, 113.0, 56.2.

***N*-(6-Chloro-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenylethane-sulfonamide (5).** A solution of **3** (2.20 g, 6.30 mmol) and **4** (3.10 g, 13.86 mmol) in DMF (50 mL) was stirred at rt for 16 h. About half of the solvent was removed under reduced pressure before the mixture was diluted with diethyl ether (50 mL). A 10% aqueous solution of citric acid (50 mL) was added. The beige suspension that formed was filtered, the collected solid was washed with water (30 mL) and diethyl ether (30 mL), and dried under high vacuum at 50 °C to give **5** (2.79 g, 89%) as a beige powder. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 497.81. ^{1}H NMR (DMSO-d_6): δ 8.99 (d, J = 4.9 Hz, 2 H), 7.64 (t, J = 4.9 Hz, 1 H), 7.20−7.26 (m, 4 H), 7.14−7.20 (m, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.02 (t, J = 7.3 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 6.61 (s br, 1 H), 3.83 (s, 3 H), 2.82−2.97 (m, 2 H).

***N*-(6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenyl-ethanesulfonamide (7).** At rt, potassium *tert*-butoxide (6.88 g, 6.03 mmol) was added portionwise to a solution of **5** (304 mg, 0.60 mmol) in ethylene glycol (10 mL) and DME (2 mL). The reaction mixture was heated to reflux for 17 h and then cooled to rt before being poured into 10% aq citric acid solution (25 mL). The mixture was extracted twice with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to give sufficiently pure **7** as an off-white solid to be used without further purification. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 524.05. ^{1}H NMR ($CDCl_3$): δ: 3.21−3.28 (m, 2 H), 3.91−3.95 (m, 2 H), 3.98 (s, 3 H), 4.29−4.38 (m, 2 H), 4.66−4.70 (m, 2 H), 6.95 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.3 Hz, 1 H), 7.13−7.30 (m, 7 H), 7.42 (t, J = 4.8 Hz, 1 H), 8.48 (s br, 1 H), 8.93−8.99 (m, 2 H).

***N*-(6-(2-((5-Bromopyrimidin-2-yl)oxy)ethoxy)-5-(2-methoxy-phenoxy)-[2,2′-bipyrimidin]-4-yl)-2-phenylethanesulfonamide (8).** To a suspension of NaH (29 mg, 0.72 mmol, 60% in mineral oil) in THF (2 mL) and DMF (2 mL), alcohol **7** (150 mg, 0.29 mmol) was added. The mixture was stirred at rt for 5 min before 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) was added. The mixture was stirred at 70 °C for 4 h before another portion of 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) and NaH (29 mg, 0.72 mmol) was added. Stirring was continued at 70 °C for 22 h before another portion of 2-chloro-5-bromopyrimidine (138 mg, 0.72 mmol) and NaH (29 mg, 0.72 mmol) was added. Stirring was continued for further 3 h before the mixture was cooled to rt and poured into 10% aq citric acid solution (75 mL). The mixture was extracted twice with ethyl acetate (2 × 50 mL). The combined extracts were washed with 10% aq citric acid solution (50 mL) and concentrated. The crude product was purified on prep TLC plates (silica gel, 0.5 mm) using ethyl acetate:methanol:7 N NH_3 in methanol 8:2:1 to give **8** (84 mg, 43%) as a pale yellow solid; R_f (silica gel, ethyl acetate:methanol:7 N NH_3 in methanol 8:2:1) 0.68. LC-MS: t_R = 0.93 min, $[M + H]^+$ = 680.01. ^{1}H NMR ($CDCl_3$) (2 conformers 1:2): δ 8.88−8.96 (m, 2 H), 8.49 (s, 1.33 H), 8.43 (s, 0.67 H), 7.50 (t, J = 5.0 Hz, 0.33 H), 7.35−

dx.doi.org/10.1021/jm3009103 | J. Med. Chem. 2012, 55, 7849−7861

UNITED THERAPEUTICS CORP., EX1006, page 401
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

7.42 (m, 0.67 H), 7.16–7.27 (m, 3.33 H), 7.01–7.15 (m, 2 H), 6.88–6.98 (m, 1.34 H), 6.79–6.87 (m, 1.67 H), 6.72–6.78 (m, 0.33 H), 5.02–5.07 (m, 0.67 H), 4.96–5.02 (m, 1.33 H), 4.72–4.77 (m, 0.67 H), 4.66–4.71 (m, 1.33 H), 4.18–4.34 (m, 1.33 H), 3.96 (s, 2 H), 3.90 (s, 1 H), 3.11–3.25 (m, 1.33 H), 2.91–3.00 (m, 0.67 H), 2.66–2.73 (m, 0.67 H). ^{13}C NMR ($CDCl_3$) (2 conformers): δ 163.48, 163.47, 161.9, 161.8, 159.5, 159.4, 157.7, 157.6, 157.5, 155.9, 150.5, 149.7, 149.4, 146.7, 145.8, 138.6, 137.7, 128.58, 128.55, 128.4, 128.2, 127.3, 126.7, 126.2, 125.2, 122.9, 122.5, 121.5, 121.2, 120.8, 115.3, 113.0, 112.4, 112.1, 112.0, 66.1, 66.0, 65.1, 64.9, 56.5, 56.0, 55.8, 55.5, 29.7, 29.6.

Potassium (*N*-Propylsulfamoyl)amide (13). Chlorosulfonyl isocyanate (**9**, 28.3 g, 0.2 mol) was dissolved in DCM (100 mL) and cooled to 0 °C before a solution of *tert*-BuOH (18.8 mL; 0.2 mol) in DCM (100 mL) was added over 30 min. Stirring was continued without cooling for additional 30 min. The mixture was then carefully added over 1 h to a solution of *n*-propylamine (16.5 mL, 0.2 mol) and triethylamine (42 mL, 0.3 mol) in DCM (400 mL) at 0 °C. Stirring was continued without cooling for additional 16 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in EtOAc (1 L) and washed with water (100 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give **11**. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7 Hz, 3 H), 1.51 (s, 9 H), 1.62 (m, 2 H), 3.04 (q, J = 6 Hz, 2 H), 5.12 (t br, J = 5 Hz, 1 H), 7.17 (s br, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.8, 28.4, 46.0, 84.1, 150.3. The residue was dissolved in dioxane (100 mL) followed by the addition of HCl in dioxane (4M; 250 mL). Stirring was continued for 4 h at rt. The solvent was evaporated under reduced pressure, and the residue was dried under HV to give sulfamide **12**. ^{1}H NMR (DMSO-d_6; 300 MHz; Varian): δ 0.87 (t, 3H), 1.43 (m, 2H), 2.81 (q, 2H), 3.09 (m, 1H; NH), 6.42 (s, 2H; NH_2). ^{13}C NMR($CDCl_3$): δ 11.6, 23.1, 45.7. The residue was dissolved in MeOH (200 mL), and KOtBu (22.4 g; 0.2 mol) was added. The solvent was removed under reduced pressure. The residue was taken up in diethylether (500 mL), and the precipitate was filtered off, washed with cold ether, and dried at HV to give potassium (*N*-propylsulamoyl)amide (**13**) (32.4 g, 92%) as an off-white powder.

5-(4-Bromophenyl)-4,6-dichloropyrimidine (14).[42] To a solution of 4-bromophenylacetic acid (73.9 g, 0.34 mol) in methanol (400 mL), thionyl chloride (49.05 g, 30 mL, 0.41 mol) was added dropwise while the temperature of the reaction mixture was kept at 0–5 °C. Upon complete addition, the cooling was removed and the mixture was allowed to warm to rt. Stirring was continued for 3 h before the solvent was removed in vacuo. The yellow oil was dissolved in benzene and evaporated. The residue was dissolved in ethyl acetate and washed with brine, 2 N aq Na_2CO_3, and again brine. The organic extract was dried over $MgSO_4$ and evaporated and dried under high vacuum at 85 °C for 30 min to give 4-bromophenylacetic acid methyl ester (74.9 g, 95%) as a yellow oil. LC-MS: t_R = 0.93 min, $[M + H]^+$ = not detectable. ^{1}H NMR (DMSO-d_6): δ 3.60 (s, 3H), 3.67 (s, 2H), 7.22 (d, J = 8.5, 2H), 7.50 (d, J = 8.5, 2H). ^{13}C NMR ($CDCl_3$): δ 40.9, 52.5, 121.4, 131.2, 131.9, 133.1, 171.6.

NaH (24.0 g, 0.82 mol, 60% in mineral oil) was suspended twice in THF (75 mL), and the solvent was decanted. The remaining slurry was diluted with THF (500 mL) and heated to 35–40 °C. A solution of 4-bromophenylacetic acid methyl ester (74.9 g, 0.33 mol) in THF (200 mL) was carefully added dropwise. Gas evolution started after about half of the phenylacetic acid ester had been added and the mixture became slightly warm. The addition was continued at 45 °C. Upon completion of the addition, stirring was continued at 40 °C for 5 min before the mixture was allowed to cool to rt. The evolution of gas had stopped before dimethylcarbonate (117.9 g, 1.31 mol) was added dropwise. Evolution of gas started, and the mixture became warm (32 °C). Upon completion of the addition, stirring of the mixture was continued for 24 h before it was cooled to 0 °C and acidified by adding 25% aq HCl (100 mL) and diluted with water (150 mL). The organic solvent was removed under reduced pressure, and the remaining aqueous mixture was extracted three times with ethyl acetate (3 × 200 mL). The organic extracts were washed with 1 N aq HCl and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was crystallized from diethyl ether/hexane. The solid material was collected, washed with cold diethyl ether/hexane, and dried under high vacuum to give 2-(4-bromophenyl)-malonic acid dimethyl ester (74.1 g, 79%) as beige crystals; mp 76–77 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.7, shows decomposition. LC-MS: this compound is not stable under HPLC conditions. ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 6 H), 4.61 (s, 1 H), 7.25–7.30 (m, 2 H), 7.46–7.51 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 53.4, 57.3, 122.9, 131.2, 131.7, 132.0, 168.2.

A solution of 2-(4-bromophenyl)-malonic acid dimethyl ester (11.73 g, 40.9 mmol) in methanol (100 mL) was added at 0 °C to a solution of sodium (2.83 g, 0.118 mmol) in methanol (100 mL). The mixture was stirred for 18 h at rt before formamidine hydrochloride (4.10 g, 50.9 mmol) was added. The suspension was stirred at rt for 4 h. The solvent was removed, and the residue was suspended in 10% aq citric acid (100 mL) and stirred for 10 min. The white precipitate was collected, washed with 10% aq citric acid, water, evaporated three times from cyclohexane, and dried under high vacuum at 40 °C to give 5-(4-bromophenyl)-pyrimidine-4,6-diol (9.90 g, 91%) as a pale-beige powder; R_f (silica gel, heptane:ethyl acetate 1:1) at start. LC-MS: t_R = 0.52 min, $[M + H]^+$ = 267.08. ^{1}H NMR (DMSO-d_6): 7.43–7.48 (m, 2 H), 7.50–7.55 (m, 2 H), 8.13 (s, 1 H), 12.1 (s br, 2 H). ^{13}C NMR (DMSO-d_6): δ 101.4, 119.3, 130.6, 132.9, 133.2, 148.7, 163.2.

To a suspension of 5-(4-bromophenyl)-pyrimidine-4,6-diol (43.0 g, 0.16 mmol) in $POCl_3$ (500 mL) was carefully added *N*,*N*-dimethylaniline (50 mL). The mixture was heated to 130 °C for 2 h. The dark-brown solution was evaporated, and the residue was dissolved in dichloromethane (200 mL). Water (500 mL) was slowly added, and the mixture was stirred at rt for 30 min before the organic phase was separated. The aqueous phase was extracted two more times with dichloromethane. The organic extracts were washed with water and 1 N aq HCl, treated with charcoal, dried over $MgSO_4$, filtered, and evaporated. The product was purified by crystallization from 2-propanol. The crystals were collected, washed with cold 2-propanol and dried under high vacuum to give **14** (39.8 g, 81%) as beige crystals; mp 100–101 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.79. LC-MS: t_R = 0.92 min, $[M + H + CH_3CN]^+$ = 344.0. ^{1}H NMR ($CDCl_3$): δ 8.81 (s, 1 H), 7.68 (dt, J_d = 8.9 Hz, J_t = 2.4 Hz, 2 H), 7.22 (dt, J_d = 9.0 Hz, J_t = 2.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 124.1, 131.0, 131.7, 132.3, 157.1, 161.4.

***N*-5-(4-Bromophenyl)-6-chloro-4-pyrimidinyl-*N*′-propylsulfamide (15).** To a solution of **14** (760 mg; 2.50 mmol) in DMSO (5 mL), the sulfamide potassium salt **13** (529 mg; 3.00 mmol) was added. The mixture was stirred at rt for 48 h, diluted with brine (25 mL), and extracted three times with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was crystallized form methanol to give **15** (706 mg, 69%) as a white solid; R_f (silica gel, heptane:ethyl acetate 1:1) 0.49. LC-MS: t_R = 0.89 min, $[M + H]^+$ = 404.98. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, J = 7.6 Hz, 3 H), 1.50–1.66 (m, 2 H), 2.94–3.03 (m, 2 H), 5.52 (s br, 1 H), 6.90 (s br, 1 H), 7.16–7.21 (m, 2 H), 7.68–7.74 (m, 2 H), 8.65 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 118.6, 125.0, 128.9, 131.2, 133.6, 156.6, 157.0, 159.9.

***N*-5-(4-Bromophenyl)-6-(2-hydroxyethoxy)-4-pyrimidinyl-*N*′-propylsulfamide (16).** Ethylene glycol (58.7 g, 53 mL; 946 mmol) was dissolved in dimethoxyethane (80 mL), and KOtBu (8.80 g; 78 mmol) was added. The temperature rose to 40 °C. After stirring for 10 min, monochloride **15** (10.55 g; 26 mmol) was added and stirring was continued at 100 °C for 70 h. The reaction mixture was carefully added to a 1:1 mixture of water:10% aq citric acid solution. The product was extracted with ethyl acetate (2 × 120 mL), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. The crude product was purified by flash column chromatography (silicagel, heptanes:ethyl acetate 1:1) to give alcohol **16** (9.65 g, 86%) as a white solid; R_f (silica gel, heptane:ethyl acetate 1:1) 0.20. LC-MS: t_R = 0.88 min, $[M + H]^+$ = 430.98. ^{1}H NMR ($CDCl_3$): δ 0.95 (t; J = 7.6 Hz, 3 H), 1.60 (h, J = 7.6 Hz, 2 H), 2.98 (t, J = 7.0 Hz, 2 H), 3.82–3.86 (m, 2 H), 4.47–4.51 (m, 2 H), 5.70 (s br, 1 H), 7.13–7.22 (m, 2 H), 7.61–7.67 (m, 2 H), 8.48 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 61.9, 69.8, 104.8, 123.8, 128.1, 131.6, 133.2, 155.9, 156.4, 166.6.

UNITED THERAPEUTICS CORP., EX1006, page 402
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

***N*-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]-ethoxy]-4-pyrimidinyl]-*N*′-propylsulfamide (17).** Sodium hydride (1.67 g, 69.6 mmol, 55% in mineral oil) was suspended twice in hexane (10 mL), and the hexane was discarded. The remaining slurry was suspended in THF (200 mL), and **16** (10.0 g, 23.2 mmol) was added in portions. The mixture was stirred for 15 min and diluted with DMF (40 mL) before 5-bromo-2-chloropyrimidine (5.38 g; 27.8 mmol) was added. The reaction mixture was heated to 60 °C, and stirring was continued for 2 h. The mixture was poured into 10% aq citric acid solution (250 mL), and the product was extracted twice with ethyl acetate (2 × 300 mL). The combined organic extracts were washed twice with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by crystallization from methanol (100 mL) to give **17** (11.99 g, 88%) as a white powder; mp 135–136 °C; R_f (silica gel, heptane:ethyl acetate 1:1) 0.44. LC-MS: t_R = 0.79 min, $[M + H]^+$ = 588.86 (major isotope). HR-LC-MS: t_R = 1.96 min; $(m + H)/z$ = 586.9711, found = 586.9714. ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 2 H), 8.49 (s, 1 H), 7.58–7.63 (m, 2 H), 7.16–7.21 (m, 2 H), 6.88 (s, 1 H), 5.61 (t, J = 6.2 Hz, 1 H), 4.72–4.76 (m, 2 H), 4.62–4.66 (m, 2 H), 2.99 (q, J = 6.8 Hz, 2 H), 1.61 (h, J = 7.3 Hz, 2 H), 0.97 (t, J = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 11.6, 22.7, 46.1, 65.3, 65.9, 104.8, 112.4, 123.7, 128.0, 131.7, 133.0, 155.7, 156.4, 159.7, 163.5, 166.3.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details on synthesis and characterization of the sulfamide and 4,6-dichloropyrimidine building blocks and the target compounds **8** and **17**–**71**. Two X-ray single crystal structures of compound **17** crystallized from different solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

The corresponding data sets have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, United Kingdom, http://www.ccdc.cam.ac.uk/, under the following deposition numbers: 888522 (crystals from methanol), 888506 (crystals from EtOAc/hexane).

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +41 61 565 65 65. Fax: + 41 61 565 65 00. E-mail: martin.bolli@actelion.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge our co-workers Nassilia Attaba, Heiner Bammerlin, Bruno Capeleto, Stephane Delahaye, Udo Diessenbacher, Fabienne Drouet, Céline Mangold, David Monnard, Pascal Rebmann, Pauline Schrepfer, Walter Schmutz, Laure Thenoz, René Vogelsanger, Daniel Wanner, and Aude Weigel for the excellent work delivered, Prof. Dr. Henri Ramuz for scientific advice, and Dr. Markus Neuburger (University of Basel) for technical advice.

■ ABBREVIATIONS USED

ABC, area between curves; CHO, Chinese hamster ovary; CSD, Cambridge Structural Database; ELSD, evaporative light scattering detector; ET, endothelin; ET_A, endothelin A receptor; ET_B, endothelin B receptor; EtOAc, ethyl acetate; KOtBu, potassium *tert*-butoxide; MAP, mean arterial pressure; SEM, standard error of the mean

■ REFERENCES

(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Goto, K.; Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* **1988**, *332*, 411–415.

(2) Battistini, B.; Botting, R. Endothelins: A Quantum Leap Forward. *Drug News Persp.* **1995**, *8*, 365–391.

(3) Kohan, D. E. Endothelin-1 and Hypertension: From Bench to Bedside. *Curr. Hypertens. Rep.* **2008**, *10*, 65–69.

(4) Thorin, E.; Clozel, M. The Cardiovascular Physiology and Pharmacology to Endothelin-1. *Adv. Pharmacol.* **2010**, *60*, 1–26.

(5) Remuzzi, G.; Perico, N.; Benigni, A. New Therapeutics that Antagonize Endothelin: Promises and Frustrations. *Nature Rev. Drug Discovery* **2002**, *1*, 986–1001.

(6) Clozel, M.; Flores, S. Endothelin Receptors as Drug Targets in Chronic Cardiovascular Diseases: The Rationale for Dual Antagonism. *Drug Dev. Res.* **2006**, *67*, 825–834.

(7) Fonseca, C.; Abraham, D.; Renzoni, E. A. Endothelin in Pulmonary Fibrosis. *Am. J. Respir. Cell Mol. Biol.* **2011**, *44*, 1–10.

(8) Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863–2867.

(9) Webb, M. L.; Meek, T. D. Inhibitors of Endothelin. *Med. Res. Rev.* **1997**, *17*, 17–67.

(10) Iglarz, M.; Clozel, M. At the heart of tissue: endothelin system and end-organ damage. *Clin. Sci.* **2010**, *119*, 453–463.

(11) Khimji, A.-K.; Rockey, D. C. Endothelin—biology and disease. *Cell. Signalling* **2010**, *22*, 1615–1625.

(12) Clozel, M.; Gray, G. A. Are There Different ET_B Receptors Mediating Constriction and Relaxation? *J. Cardiovasc. Pharmacol.* **1995**, *26*, S262–S264.

(13) Harada, N.; Himeno, A.; Shigematsu, K.; Sumikawa, K.; Niwa, M. Endothelin-1 Binding to Endothelin Receptors in the Rat Anterior Pituitary Gland: Possible Formation of an ET_A–ET_B Receptor Heterodimer. *Cell. Mol. Neurobiol.* **2002**, *22*, 207–226.

(14) Gregan, B.; Jürgensen, J.; Papsdorf, G.; Furkert, J.; Schaefer, M.; Beyermann, M.; Rosenthal, W.; Oksche, A. Ligand-Dependent Differences in the Internalization of Endothelin A and Endothelin B Receptor Heterodimers. *J. Biol. Chem.* **2004**, *279*, 27679–27987.

(15) Sauvageau, S.; Thorin, E.; Villeneuve, L.; Dupuis, J. Change in pharmacological effect of endothelin receptor antagonists in rats with pulmonary arterial hypertension: Role of ET_B-receptor expression levels. *Pulm. Pharmacol. Ther.* **2009**, *22*, 311–317.

(16) Iglarz, M.; Clozel, M. Mechanisms of ET-1-induced Endothelial Dysfunction. *J. Cardiovasc. Pharmacol.* **2007**, *50*, 621–628.

(17) Dagassan, P. H.; Breu, V.; Clozel, M.; Künzli, A.; Vogt, P.; Turina, M.; Kiowski, W.; Clozel, J.-P. Up-Regulation of Endothelin-B Receptors in Atherosclerotic Human Coronary Arteries. *J. Cardiovasc. Pharmacol.* **1996**, *27*, 147–153.

(18) Abraham, D. J.; Vancheeswaran, R.; Dashwood, M. R.; Rajkumar, V. S.; Pantelides, P.; Shi-wen, X.; du Bois, R. M.; Black, C. M. Increased Levels of Endothelin-1 and Differential Endothelin Type A and B Receptor Expression in Scleroderma-Associated Fibrotic Lung Disease. *Am. J. Pathol.* **1997**, *151*, 831–841.

(19) Bauer, M.; Wilkens, H.; Langer, F.; Schneider, S. O.; Lausberg, H.; Schäfers, H.-J. Selective Upregulation of Endothelin B Receptor Gene Expression in Severe Pulmonary Hypertension. *Circulation* **2002**, *105*, 1034–1036.

(20) Saleh, D.; Furukawa, K.; Tsao, M.-S.; Maghazachi, A.; Corrin, B.; Yanagisawa, M.; Barnes, P. J.; Giaid, A. Elevated Expresseion of Endothelin-1 and Endothelin-converting Enzyme-1 in Idiopathic Pulmonary Fibrosis: Possible Involvement of Proinflammatory Cytokines. *Am. J. Respir. Cell Mol. Biol.* **1997**, *16*, 187–193.

(21) Lehrke, I.; Waldherr, R.; Ritz, E.; Wagner, J. Renal endothelin-1 and endothelin receptor type B expression in glomerular diseases with proteinuria. *J. Am. Soc. Nephrol.* **2001**, *12*, 2321–2329.

UNITED THERAPEUTICS CORP., EX1006, page 403
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

(22) Wu-Wong, J. R.; Padley, R. Endothelin receptor antagonists: A clinical study up-date. *Curr. Opin. Cardiovasc. Pulm. Renal Invest. Drugs* **2000**, *2*, 339–344.
(23) Wu, C. Recent discovery and development of endothelin receptor antagonists. *Exp. Opin. Ther. Patent* **2000**, *10*, 1653–1668.
(24) Boss, C.; Bolli, M.; Weller, T. Endothelin Receptor Antagonists: Structures, Synthesis, Selectivity and Therapeutic Applications. *Curr. Med. Chem.* **2002**, *9*, 349–383.
(25) Iqbal, J.; Sanghi, R.; Das, S. K. Endothelin Receptor Antagonists: An Overview of Their Synthesis and Structure–Activity Relationship. *Mini-Rev. Med. Chem.* **2005**, *5*, 381–408.
(26) Aubert, J.-D.; Juillerat-Jeanneret, L. Therapeutic potential of endothelin receptor modulators: lessons from human clinical trials. *Expert Opin. Ther. Targets* **2009**, *13*, 1069–1084.
(27) Houde, M.; Labonté, J.; D'Orléans-Juste, P. Peptide and Non-peptide Antagonists Targeting Endothelin Receptors in Physiology and Pathology. *Curr. Pharm. Des.* **2011**, *17*, 2613–2625.
(28) Hoette, S.; O'Callaghan, D. S.; Jardim, C.; Souza, R. Dual receptor blockade by bosentan: clinical experience in treatment of pulmonary hypertension. *J. Recept., Ligand Channel Res.* **2010**, *3*, 113–121.
(29) Dwyer, N.; Kilpatrick, D. Bosentan for the treatment of adult pulmonary hypertension. *Future Cardiol.* **2011**, *7*, 19–37.
(30) *Tracleer*; European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000401/human_med_001100.jsp&murl=menus/ (Accessed May 2012).
(31) Blalock, S. W.; Matulevicius, S.; Mitchell, L. C.; Reimold, S.; Warner, J.; Peshock, R.; Torres, F.; Chin, K. M. Long-Term Outcomes With Ambrisentan Monotherapy in Pulmonary Arterial Hypertension. *J. Card. Failure* **2010**, *16*, 121–127.
(32) Frampton, J. E. Ambrisentan. *Am. J. Cardiovasc. Drugs* **2011**, *11*, 215–226.
(33) *Volibris*; European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000839/human_med_001151.jsp&mid=WC0b01ac058001d124 (Accessed May 2012).
(34) Goligorsky, M. S.; Iijima, K.; Morgan, M.; Yanagisawa, M.; Masaki, T.; Lin, L.; Nasjletti, A.; Kaskel, F.; Frazer, M.; Badr, K. F. Role of Endothelin in the Development of Dahl Hypertension. *J. Cardiovasc. Pharmacol.* **1991**, *17*, S484–S491.
(35) Doucet, J.; Gonzalez, W.; Baptiste, J. Endothelin Antagonists in Salt-Dependent Hypertension Associated with Renal Insufficiency. *J. Cardiovasc. Pharmacol.* **1996**, *27*, 643–651.
(36) Schiffrin, E. L. Role of endothelin-1 in hypertension and vascular disease. *Am. J. Hypertens.* **2001**, *14*, 83S–89S.
(37) Fattinger, K.; Funk, C.; Pantze, M.; Weber, C.; Reichen, J.; Stieger, B.; Meier, P. J. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: A potential mechanism for hepatic adverse reactions. *Clin. Pharmacol. Ther.* **2001**, *69*, 223–231.
(38) Neidhart, W.; Breu, V.; Burri, K.; Clozel, M.; Hirth, G.; Klinkhammer, U.; Giller, T.; Ramuz, H. Discovery of Ro 48–5695: A Potent Mixed Endothelin Receptor Antagonist Optimized from Bosentan. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2223–2228.
(39) Harrington, P. J.; Khatri, H. N.; DeHoff, B. S.; Guinn, M. R.; Boehler, M. A.; Glaser, K. A. Research and Development of a Second-Generation Process for Bosentan, an Endothelin Receptor Antagonist. *Org. Process Res. Dev.* **2002**, *6*, 120–124.
(40) Bolli, M.; Boss, C.; Fischli, W.; Clozel, M.; Weller, T. Novel Sulfamides and Their Use as Endothelin Receptor Antagonists. WO2002053557, Jul 11, 2002.
(41) Bolli, M. H.; Boss, C.; Clozel, M.; Fischli, W.; Hess, P.; Weller, T. The Use of Sulfonylamido Pyrimidines Incorporating an Unsaturated Side Chain as Endothelin Receptor Antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 955–959.
(42) Boss, C.; Fischli, W.; Weller, T.; Clozel, M.; Bolli, M. Novel Sulfamides. WO2006051502, May 18, 2006.
(43) Burri, K.; Clozel, M.; Fischli, W.; Hirth, G.; Löffler, B. M.; Ramuz, H. Verwendung von Sulfonamiden als Heilmittel und neue Sulfonamide. EP0510526, Oct 28, 1992.
(44) Burri, K.; Clozel, M.; Fischli, W.; Hirth, G.; Löffler, B.-M.; Ramuz, H.; Neidhart, W. Sulfonamide, ihre Herstellung und Verwendung als Heilmittel und Zwischenprodukte. EP0526708, Feb 10, 1993.
(45) Yamada, K.; Yasuda, K.; Kikkawa, K.; Kohno, R. Sulfonamide derivative and process for preparing the same. EP0743307, Nov 20, 1996.
(46) Yamada, K.; Yasuda, K.; Kikkawa, K.; Kohno, R. Sulfonamide Derivate und Verfahren zu deren Herstellung. EP0959072, Oct 31, 2002.
(47) Bolli, M.; Boss, C.; Clozel, M.; Fischli, W.; Weller, T. Pyrimidine-Sulfamides and Their Use as Endothelin Receptor Antagonist. WO2004050640, Jun 17, 2004.
(48) Brown, D. J.; Lyall, J. M. Pyrimidine Reactions. *Aust. J. Chem.* **1964**, *17*, 794–802.
(49) Crosby, D. G.; Berthold, R. V. *n*-Butyl 5-Chloro-2-pyrimidoxyacetate—A Plant Growth Regulator Analog. *J. Org. Chem.* **1960**, *25*, 1916–1919.
(50) Maggiali, C.; Morini, G.; Mossini, F.; Morini, G.; Barocelli, E. H1-antihistaminic and antimuscarinic effects of 2- and 4-[benzyl-(2-dimethylaminoethyl)amino]pyrimidine compounds. *Farmaco, Ed. Sci.* **1988**, *43*, 277–292.
(51) Wacker, D. A.; Rossi, K. A.; Wang, Y. Preparation of pyridones as GPR119 G protein-coupled receptor agonists. WO2009012275, Jan 22, 2009.
(52) Yamanaka, H.; Takekawa, T.; Morita, K.; Ishihara, T.; Gupton, J. T. Preparation of novel β-trifluoromethyl vinamidinium salt and its synthetic application to trifluoromethylated heterocycles. *Tetrahedron Lett.* **1996**, *37*, 1829–1832.
(53) Morimoto, H.; Ohashi, N.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Potent and Selective ET-A Antagonists. 2. Discovery and Evaluation of Potent Water Soluble *N*-(6-(2-Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives. *J. Med. Chem.* **2001**, *44*, 3369–3377.
(54) Clozel, M.; Breu, V.; Burri, K.; Cassal, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. *Nature* **1993**, *365*, 759–761.
(55) Neidhart, W.; Breu, V.; Bur, D.; Burri, K.; Clozel, M.; Hirth, G.; Müller, M.; Wessel, H. P.; Ramuz, H. The Discovery of Nonpeptide Endothelin Receptor Antagonists. Progression towards Bosentan. *Chimia* **1996**, *50*, 519–524.
(56) Breu, V.; Burri, K.; Cassal, J.-M.; Clozel, M.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. Novel Sulfonamides. WO9619459, Jun 27, 1996.
(57) Morimoto, H.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Potent and Selective ET-A Antagonists. 1. Synthesis and Structure–Activity Relationship of *N*-(6-(2-Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives. *J. Med. Chem.* **2001**, *44*, 3355–3368.
(58) Morimoto, H.; Shimadzu, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. Modifications and Structure–Activity Relationships at the 2-Position of 4-Sulfonamido-pyrimidine Derivatives as Potent Endothelin Antagonists. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 81–84.
(59) Brockway, B. P.; Mills, P. A.; Azar, S. H. A New Method for Continuous Chronic Measurement and Recording of Blood Pressure, Heart Rate and Activity in the Rat via Radio-Telemetry. *Clin. Exp. Hypertens.—Theory Pract* **1991**, *A13*, 885–895.
(60) Guiol, C.; Ledoussal, C.; Surgé, J.-M. A Radiotelemetry System for Chronic Measurement of Blood Pressure and Heart Rate in the Unrestrained Rat Validation of the Method. *J. Pharmcol. Toxicol. Methods* **1992**, *28*, 99–105.
(61) Hess, P.; Clozel, M.; Clozel, J.-P. Telemetry monitoring of pulmonary arterial pressure in freely moving rats. *J. Appl. Physiol.* **1996**, *81*, 1027–1032.

UNITED THERAPEUTICS CORP., EX1006, page 404
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

(62) Iglarz, M.; Binkert, C.; Morrison, K.; Fischli, W.; Gatfield, J.; Treiber, A.; Weller, T.; Bolli, M. H.; Boss, C.; Buchmann, S.; Capeleto, B.; Hess, P.; Qiu, C.; Clozel, M. Pharmacology of Macitentan, an Orally Active Tissue-Targeting Dual Endothelin Receptor Antagonist. *J. Pharmacol. Exp. Ther.* **2008**, *327*, 736−745.
(63) Sidharta, P. N.; van Giersbergen, P. L. M.; Halabi, A.; Dingemanse, J. Macitentan: entry-into-humans study with a new endothelin receptor antagonist. *Eur. J. Clin. Pharmacol.* **2011**, *67*, 977−984.
(64) Gabbay, E.; Fraser, J.; McNeil, K. Review of bosentan in the management of pulmonary arterial hypertension. *Vasc. Health Risk Manage.* **2007**, *3*, 887−900.
(65) Dhillon, S.; Keating, G. M. Bosentan—A Review of its Use in the Management of Mildly Symptomatic Pulmonary Arterial Hypertension. *Am. J. Cardiovasc. Drugs* **2009**, *9*, 331−350.
(66) Dhillon, S. Bosentan—A Review of its Use in the Management of Digital Ulcers Associated with Systemic Sclerosis. *Drugs* **2009**, *69*, 2005−2024.
(67) *Study of ACT-064992 on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT00660179 (Accessed May 2012).
(68) *Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-1)*; ClinicalTrials.gov,, http://clinicaltrials.gov/ct2/show/NCT01474109 (Accessed May 2012).
(69) *Macitentan for the Treatment of Digital Ulcers in System Sclerosis Patients (DUAL-2)*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT01474122 (Accessed May 2012).
(70) *Macitentan in Combo With Dose-dense Temozolomide in Patients With Recurrent Glioblastoma*; ClinicalTrials.gov, http://clinicaltrials.gov/ct2/show/NCT01499251 (Accessed May 2012).
(71) Zhong, Z.; Bibbs, J. A.; Yuan, W.; Wong, C.-H. Active-Site-Directed Modification of Subtilisin. *J. Am. Chem. Soc.* **1991**, *113*, 2259−2263.

UNITED THERAPEUTICS CORP., EX1006, page 405
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Acknowledgement Receipt

EFS ID:	17767877
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La/Stephanie Owusu-Hemeng
Filer Authorized By:	Brittany La
Attorney Docket Number:	AC-66-USC
Receipt Date:	27-DEC-2013
Filing Date:	05-SEP-2012
Time Stamp:	14:20:52
Application Type:	Utility under 35 USC 111(a)

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	Appeal Brief Filed	AC66USC_APPEAL_BRIEF_12272013.pdf	1404302 c4cd9942ae7b3279e2c301912440ef4932b3fc0c	no	28

Warnings:	
Information:	

Total Files Size (in bytes):	1404302

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 01/21/2014

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 01/21/2014

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

PTO-90C (Rev. 10/03)

Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No. 13/604,148	Applicant(s) Martine Clozel	
	Examiner Kendra D. Carter	Art Unit 1627	

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

The Appeal Brief filed on *December 27, 2013* is defective for failure to comply with one or more provisions of 37 CFR 41.37(c).

To avoid dismissal of the appeal, applicant must file an amended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☐ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☒ (a) The brief does not contain a concise explanation of the subject matter defined in each of the rejected independent claims, referring to the specification in the Record by page and line number or by paragraph number and to the drawings, if any, by reference characters; and/or (b) the brief fails to identify, for each rejected independent claim and for each dependent claim argued separately that contains a means plus function or step plus function recitation under 35 U.S.C. 112, sixth paragraph, the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification in the Record by page and line number or paragraph number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(iii)).

3. ☒ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(v)).

4. ☒ Other (including any explanation in support of the above items):

Section III (Section V) Summary of Claimed Subject Matter must identify and map all independent claims separately on appeal to the Specification by page and line number or paragraph number if used in the original specification and drawings if any by reference characters. (Claims 1, 12, 13, and 14 were not mapped).

The Claims Appendix is deficient as it does not match the last entered amendment filed. Specifically claims 2, 3, 4, and 7-11 (i.e., a method according to claim 0).

Another brief in its entirety is not required, just the corrected section.

Sonja Despertt, Supervisory Paralegal
(571) 272-9797

UNITED THERAPEUTICS CORP., EX1006, page 409
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

Response to Notification of Non-Compliant Appeal Brief

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

In response to the Notification of Non-Compliant Appeal Brief mailed January 21, 2014, Appellants submit herewith the amended "Summary of Claimed Subject Matter" to provide the page and line or paragraph number in the original specification for independent claims 1, 12, 13 and 14. Appellants also provide herewith the amended Claims Appendix to correct the typographical errors in claims 2, 3, 4 and 7-11. Only the corrected sections of the appeal brief is provided herewith.

It is believed no fees are due. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 50-4255.

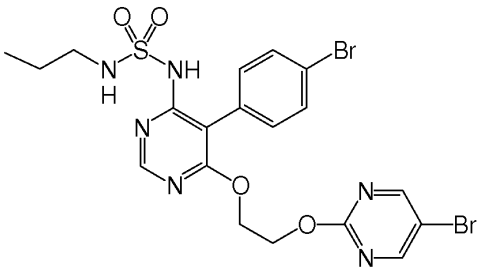
Respectfully Submitted,

Date: February 21, 2014

By: */Brittany La/*
Brittany La
Reg. No. 58,337
Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
(973) 912-5232

III. SUMMARY OF CLAIMED SUBJECT MATTER

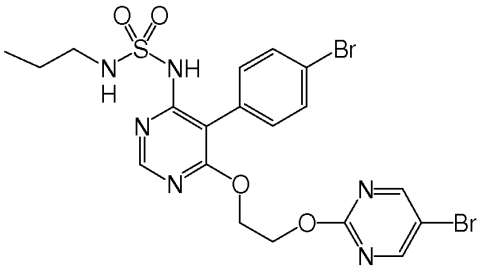
Claims 1-14 are pending and stand rejected. Independent claim 1 is directed to a method for the treatment of hypertension, pulmonary hypertension or pulmonary arterial hypertension, comprising administering simultaneously, separately or over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form. *See page 1, lines 1-6 (also page 6, lines 1-8); page 5, lines 22 and 26-27.*

Independent claim 12 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

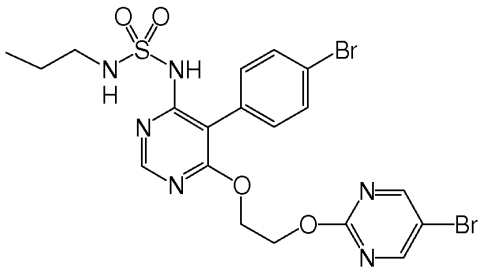


(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form. *See page 1, lines 1-6 (also page 6, lines 1-8); page 5, lines 4-7; page 4, lines 10-12.*

Independent claim 13 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

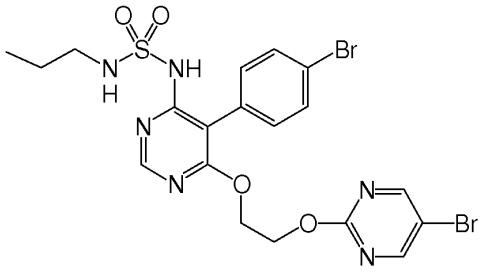
UNITED THERAPEUTICS CORP., EX1006, page 411
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form. *See page 1, lines 1-6 (also page 6, lines 1-8); page 5, lines 4-7; page 4, lines 13-15.*

Independent claim 14 is directed to a method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



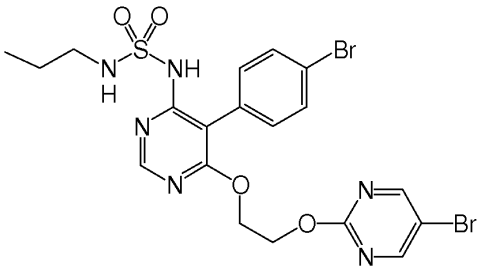
(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form. *See page 1, lines 1-6 (also page 6, lines 1-8); page 5, lines 4-17; page 1, line 5.*

UNITED THERAPEUTICS CORP., EX1006, page 412
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

CLAIMS APPENDIX

1. (Previously Presented) 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):



(I)

in free or pharmaceutically acceptable salt form, and at least one compound having PDE5-inhibitory properties, in free or pharmaceutically acceptable salt form.

2. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered simultaneously.

3. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered separately.

4. (Previously Presented) The method according to claim 1, wherein the compound of formula (I) and the compound having PDE5-inhibitory properties are administered over a period of time.

5. (Previously Presented) The method according to claim 4, wherein the administration of the compound of formula (I) will be alternated with the administration of a compound having PDE5-inhibitory properties, and the interval between such administration will not exceed two or three days.

UNITED THERAPEUTICS CORP., EX1006, page 413
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

6. (Previously Presented) The method according to claim 5, wherein said administration will not exceed one day.

7. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is selected from sildenafil, vardenafil, tadalafil and udenafil.

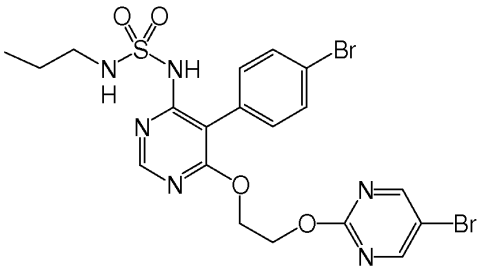
8. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is sildenafil.

9. (Previously Presented) The method according to claim 1, wherein the compound having PDE5-inhibitory properties is tadalafil.

10. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary hypertension.

11. (Previously Presented) The method according to claim 1, wherein the disease intended to be treated is pulmonary arterial hypertension.

12. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, simultaneously, an effective amount of a compound of formula (I):

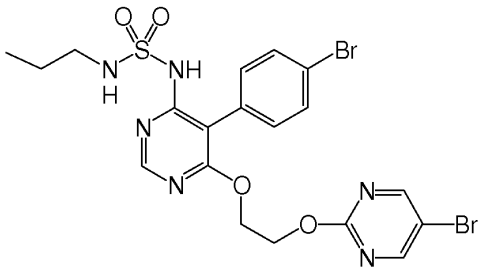


(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

13. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering over a period of time, to a patient in need thereof, an effective amount of a compound of formula (I):

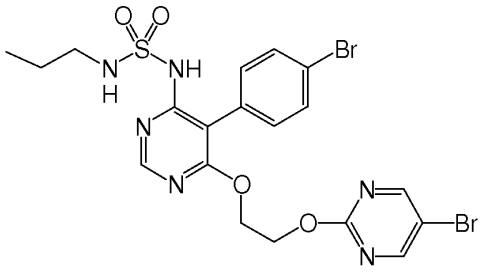
UNITED THERAPEUTICS CORP., EX1006, page 414
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

14. (Previously presented) A method for the treatment of pulmonary arterial hypertension, comprising administering to a patient in need thereof, separately, an effective amount of a compound of formula (I):



(I)

in free or pharmaceutically acceptable salt form, and at least one of sildenafil or tadalafil, in free or pharmaceutically acceptable salt form.

UNITED THERAPEUTICS CORP., EX1006, page 415
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

Miscellaneous Communication

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

Applicants submit herewith a Supplemental Application Data Sheet to correct an error in priority information noted in the original Application Data Sheet submitted on September 5, 2012. Application PCT/IB2006/052999 and PCT/IB2006/053857 has been deleted from the Domestic Benefit/National Stage Information Section of the Supplemental Application Data Sheet and has been added to the Foreign Priority Information Section of the Supplemental Application Data Sheet. It is noted that priority is correctly claimed in this application as it is correctly noted in the Combined Declaration and Power of Attorney form submitted on September 5, 2012 as well as accurately reflected in the Filing Receipt mailed September 25, 2012. Applicants further note that this priority information is consistent with the information in parent U.S. Application No. 12/439,290. Therefore, the Supplemental Application Data Sheet simply makes consistent the priority information on records. Applicants earnestly request acceptance of the Supplemental Application Data Sheet submitted herewith.

It is believed no fees are due. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to Deposit Account No. 50-4255.

Respectfully Submitted,

Date: __February 21, 2014_____

By: ___*/Brittany La/*_____

Brittany La
Reg. No. 58,337
Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
(973) 912-5232

UNITED THERAPEUTICS CORP., EX1006, page 417
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Supplemental **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	AC-66-USC
	Application Number	13/604,148
Title of Invention	THERAPEUTIC COMPOSITIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Martine		CLOZEL	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Binnigen	Country Of Residence	CH
Citizenship under 37 CFR 1.41(b)	FR		

Mailing Address of Applicant:

Address 1	Winterhalde 3b		
Address 2			
City	Binnigen	State/Province	
Postal Code	CH-4102	Country	CH

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	50446		
Email Address	~~file@hoxpat.com~~ hoxiepatentmail@hoxpat.com	Add Email	Remove Email

Application Information:

Title of the Invention	THERAPEUTIC COMPOSITIONS		
Attorney Docket Number	AC-66-USC	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Supplemental **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	AC-66-USC
	Application Number	13/604,148
Title of Invention	THERAPEUTIC COMPOSITIONS	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	50446		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13604148	Continuation of	12439290	2009-02-27
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12439290	a 371 of international	PCT/IB2007/053448	2007-08-28
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
~~PCT/IB2007/053448~~	~~non-provisional of~~	~~PCT/IB2006/052999~~	~~2006-08-29~~
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
~~PCT/IB2007/053448~~	~~non-provisional of~~	~~PCT/IB2006/053857~~	~~2006-10-19~~

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

PTO/SB/14 (11-08)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Supplemental **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	AC-66-USC
	Application Number	13/604,148
Title of Invention	THERAPEUTIC COMPOSITIONS	

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
PCT/IB2006/052999	IB	2006-08-29	(•) Yes ( ) No

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
PCT/IB2006/053857	IB	2006-10-19	(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	Actelion Pharmaceuticals Ltd.		
Mailing Address Information:			
Address 1	Gewerbestrasse 16		
Address 2			
City	Allschwil	**State/Province**	
Country	CH	Postal Code	CH-4123
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Brittany La/			Date (YYYY-MM-DD)	2014-02-21
First Name	Brittany	Last Name	LA	Registration Number	58337

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED THERAPEUTICS CORP., EX1006, page 421
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Acknowledgement Receipt	
EFS ID:	18263092
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Brittany La
Filer Authorized By:	
Attorney Docket Number:	AC-66-USC
Receipt Date:	21-FEB-2014
Filing Date:	05-SEP-2012
Time Stamp:	11:37:03
Application Type:	Utility under 35 USC 111(a)

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	Supplemental Appeal Brief	AC66USC_Response_to_Notice_of_NonCompliant_Appeal_Brief.pdf	44680 e8110751e1dd661607e7466c140dad21a4e6cd90	no	6

Warnings:
Information:

2	Miscellaneous Incoming Letter	AC-66-USC_Miscellaneous_Communication_Feb_18_2014.pdf	20807 a5371d8bea3f700d425a93f9e2e363cfc302ebcb	no	2
Warnings:					
Information:					
3	Application Data Sheet	AC66USC_SUPPADS_02212014.pdf	118238 49a8d8d527da360030ec2344c789ae1406dd8fc5	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
			Total Files Size (in bytes):	183725	

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 06/26/2014

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/26/2014	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Application Number: 13/604,148
Filing Date: 09/05/2012
Appellant(s): Clozel, Martine

Brittany La
(Reg. No. 58,337)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 21, 2014.

(1) Grounds of Rejection to be Reviewed on Appeal

Every ground of rejection set forth in the Office action dated June 20, 2013 from which the appeal is taken is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The following ground(s) of rejection are applicable to the appealed claims.

1) Claims 1-14 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 or sildenafil to treat pulmonary hypertension or pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be 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 combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

2) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 10 and 18 of copending Application No. 12/388,142 ('142) (recently allowed) 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 to treat pulmonary arterial hypertension.

The Application ‘142 does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not

exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to combine the compound of Formula I and a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary 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 combined to treat pulmonary hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

3) Claims 1-14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent 8,268,847 ('847) in view of Bolli et al. (WO 02/053557 A1) and Keyser et al. (WO 2006/026395 A1).

The Patent '847 teaches a composition of formula I with a PDE5 inhibitor such as tadalafil and sildenafil to treat pulmonary hypertension.

The Patent '847 does not teach the treatment of pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43).

The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious to treat pulmonary arterial hypertension with the combination because Keyser et al. teach that an ET antagonist and PDE5 inhibitors such as sildenafil and tadalafil can be combined to treat pulmonary arterial hypertension.

To one skilled in the art it would be obvious to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to

achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23)

4) Claims 1-14 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, portal hypertension, pulmonary hypertension and erectile dysfunction (see abstract and pages 16-17).

Bolli et al. does not teach the composition with a PDE-5 inhibitor such as tadalafil or sildenafil to treat pulmonary arterial hypertension, nor the administration schedule of claims 2-6 and 12-14.

Keyser et al. teach that ET antagonist and PDE5 inhibitors such as tadalafil or sildenafil are combined together to treat cardiac disorders such as hypertension and pulmonary hypertension (see abstract, paragraph 30 and claims 15, 19, 21, 25 and 26). Pulmonary hypertension relates to pulmonary arterial hypertension (see paragraph 43). The administration of the ET antagonist and the PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72).Both or separately, the drugs can be

administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

To one skilled in the art it would be obvious and motivated 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 combined to treat pulmonary hypertension, hypertension and pulmonary arterial hypertension.

To one skilled in the art it would be obvious and motivated to administer the compound of Formula I and the PDE5 inhibitor simultaneously, separately, over a period of time, or such that administration of the two drugs are separate but do not exceed one, two or three days between each other because Keyser et al. teach that an ET antagonist and PDE5 inhibitor can be formulated together or formulated separately and administered concurrently or sequentially (i.e. simultaneously or separately; see paragraphs 20, 25 and 32). Keyser et al. also teach that sequential can include administration every other day treatment of agent and daily administration of the other agent as required to achieve therapeutic effect (i.e. alternated with interval not exceeded by one or two days; see paragraph 72). Keyser et al. also teach both or separately, the drugs can be administered in a controlled release formulation (i.e. administered over a period of time; see paragraphs 21 and 23).

(2) Response to Argument

The Appellant argues that there is no motivation to select the instant compound of Formula (I) from page 28 of Bolli to combine with PDE5 inhibitor of Keyser because said compound of formula (I) is not the lead compound and is not taught to be ET_A selective. Neither general disclosure nor mere identification in the prior art of each component of a composition can establish that the combination as a whole would have been obvious. The Examiner is effectively arguing that because Keyser teaches a broad genus, all species that fall under that genus would be obvious. This argument, however, has been rejected by the Federal Circuit. Therefore, identification of a genus does not render the species prima facie obvious. If the analysis were to start with Keyser, one skill in the art would not select example 104 from Bolli as a lead compound out of the universe of ET_A compounds because Keyser does not point to Bolli. If the analysis were to start with Bolli, the most preferred compounds are identified on page 23. Even if Example 104 were chosen as the lead, there is no motivation to modify the lead compound to arrive at the compound of formula (I) claimed herein. Appellant respectfully disagrees that one skilled in the art would expect the activity ratio of the compound on page 28 to be similar to the N-ethyl analog of Example 104. Biological activities are generally unpredictable and cannot be extrapolated in the abstract as the Examiner did. Selecting the compound of Appellant's claims from Bolli would require choosing it from among the over 200 Bolli examples, without the benefit of any ET_A and ET_B inhibition data. Such a selection could only be made using impermissible hindsight, with Appellant's disclosure as a guide. Keyser specifically teaches away from using a compound having non-selective ET activity, particularly compounds having ET_B antagonistic activity. One skilled in the art would not be motivated to choose the compound of Example 104, which has ET_B activity, as the lead compound. One skilled in the art also would not select the second compound on page 28 of Bolli to be combined with Keyser because if one presumes activity to be similar to Example 104, the combination would not be an ideal choice. The present invention is also not obvious because it produces an unexpected effect. According to Keyser, a compound which has ET_B antagonistic activity is expected to interfere with vasodilation and therefore is expected to be less effective in combination with a PDE5 inhibitor. The claimed compound has an in vitro ET_A:ET_B antagonistic activity of about 1:782. Thus like Bosentan, it is considered to be a dual ET_A-ET_B receptor antagonist. Keyser teaches

> away from the use of dual ET_A-ET_B receptor antagonists. Appellant has surprisingly found that the combination of the compound of formula I with a PDE5-inhibitor results in an unexpected effect in the treatment of diseases wherein vasoconstriction is involved. Greater than the sum of the ABC values for administration of either component alone was shown in the specification. Keyser does not show any unexpected result at all. The Examiner failed to consider the unexpected results. As discussed above, there is no motivation to combine the compound claimed in the '142 application or the '781 patent with a PDE5 inhibitor as Keyser teaches away from this combination. The Appellant will consider filing a terminal disclaimer over the '847 patent upon an indication of allowable subject matter.

The Examiner disagrees because first, the combination of a ET antagonist and a PDE5 inhibitor such as tadalafil or sildenafil to treat cardiac disorders such as hypertension and pulmonary hypertension is known according to the teachings of Keyser et al. (see paragraph 30 and claims 15, 19, 21, 25 and 26). Second, Keyser et al. defines selective compounds for ET_A antagonist should display a relative receptor binding ratio of at least 100 (see paragraph 59). One skilled in the art may start with those compounds with the highest ET_A selectivity but that does not preclude trying all compounds similar and/or those that fall within the definition of Keyser et al. Keyser et al. also teaches that bosentan is considered nonselective because it has an ET_A:ET_B selectivity ratio of 20 (see paragraph 60). Third, according to Bolli et al. the ethyl analog of the Applicants claimed compound has a ET_A:ET_B selectivity ratio of 682.95 (see page 93, compound 104; and page 6). Thus, the compound is much more selective for ET_A than ET_B, far from being considered as nonselective compared to bosentan, and fits the definition of an ET_A antagonist by Keyser et al. Further, one skilled in the art would be motivated to choose all the compounds of Bolli et al. that have greater selectivity for ET_A

over ET_B with reasonable expectation of success and motivation that the combination with a PDE5 inhibitor would provide treatment for conditions such as hypertension and pulmonary hypertension. Selection of a known material based on its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the Applicant's specific selection. See e.g., *In re Leshin*, 227 F.2d 197, 125 USPQ 416 (CCPA 1960). Although the specific claimed compound is taught by Bolli et al. but not tested for its ET_A:ET_B selectivity ratio one would expect it to be similar to the N-ethyl analog compound 104. Bolli et al. is not required to test every compound disclosed, but Bolli et al. provides tests for a representation of compounds disclosed. Compounds that are homologs (compounds differing regularly by the successive addition of the same chemical group), e.g., by –CH2- groups are generally of sufficiently close structural similarity that there is presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457,195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d1082,197USPQ 601 (CCPA 1978). 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.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/KENDRA D CARTER/

Primary Examiner, Art Unit 1627

Conferees:

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

/Larry R. Helms/

Primary Examiner

Requirement to pay appeal forwarding fee. In order to avoid dismissal of the instant appeal in any application or ex parte reexamination proceeding, 37 CFR 41.45 requires payment of an appeal forwarding fee within the time permitted by 37 CFR 41.45(a), unless appellant had timely paid the fee for filing a brief required by 37 CFR 41.20(b) in effect on March 18, 2013.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

Applicant:	Martine CLOZEL	Examiner:	CARTER, Kendra D.
Serial No.:	13/604,148	Group Art Unit:	1627
Filed:	September 5, 2012	Confirmation No.:	5499
Title:	THERAPEUTIC COMPOSITIONS	Docket:	AC-66-USC

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

REPLY BRIEF UNDER 37 C.F.R. § 41.37

This Reply Brief is being submitted in response to the Examiner's Answer filed on June 26, 2014.

For the reasons stated herein and in the Appeal Brief, Appellants respectfully request reversal of the Final Rejection mailed on June 20, 2013, and remand for allowance of the pending claims.

ARGUMENT

A. Rejection under 35 U.S.C. § 103(a)

1. The Examiner's selection of the instant compound of Formula (I) from page 28 of Bolli et al. as a lead compound is erroneous.

a. There were many other selective ET_A antagonists to choose from besides those in Bolli et al.

The Examiner argues that it would be obvious to select any Bolli et al. compound with an ET_A selectivity within the Keyser definition as a lead compound, stating that "[o]ne skilled in the art may start with those compounds with the highest ET_A selectivity but that does not preclude trying all compounds similar and/or those that fall within the definition of Keyser et al." Examiner's Answer at page 13. However, those of skill in the art had numerous selective ET_A antagonists to select from besides those disclosed in Bolli et al. For example, Applicants respectfully direct the Board's attention to Battistini et al., Exp. Biol. Med. (2006), 231(6), 653-695 (hereafter "Battistini et al."), which is a contemporaneous review article illustrating the endothelia receptor antagonist landscape in 2006. Battistini et al. discloses the structures of ten selective ETA antagonists are shown on page 660, and discusses them on pages 659, 661 and 678. Following the Examiner's logic, the skilled artisan would have considered the selective ETA antagonists known in the art, for example as mentioned at page 660 of the Battistini et al. review, since it was taught that these selective ETA antagonists would have favorable properties for use in man.

In addition, if those of skill in the art were to have adopted the Examiner's proposed criteria for selecting an ET_A antagonist for use in combination with a PDE5 inhibitor; i.e., those meeting the Keyser et al. definition of having an ET_A/ ET_B selectivity ratio of at least 100, then the result would be to actually ***exclude*** the non-preferred compounds in Bolli et al., but at the same time go beyond the compounds listed in Bolli et al. to ***include*** many other compounds known in the art as selective ET_A antagonists, any of which would be more obvious candidates for combination with a PDE5 inhibitor under the rationale of Bolli et al. Examples of such selective ET_A antagonists include those referred to above in the Battistini et al. article, and in the numerous references listed in paragraph [0048] of the Keyser et al. reference, which are said to

UNITED THERAPEUTICS CORP., EX1006, page 441
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

disclose possible ET_A antagonists that would potentially be suitable for use in combination with PDE5 inhibitors such as sildenafil or tadalafil.

The Board must take into account the scope of this class of compounds, as it would have been understood by one of skill in the art, as evidenced by contemporary reviews such as Battistini et al., and the disclosure of numerous potential selective ET_A antagonists of the Keyser et al. references. This class would not have been understood to include compounds such as Example 104 of Bolli et al., which Bolli et al. did not identify as being preferred or unusually selective, and certainly could not have included Macitentan, which was not characterized in Bolli et al. or identified anywhere in any art cited as being a "selective ET_A antagonist" or a compound that falls within the definition of Keyser et al. Thus it can be seen that the skilled artisan would have had no motivation to select any of the Bolli et al. compounds over the Battistini et al. and/or Keyser compounds.

b. Even within Bolli et al. , there is no motivation to select Macitentan as a lead compound

Even if one were to limit the universe of possible ET_A antagonists for use in combination with PDE5 inhibitors to those disclosed in Bolli et al. (and there was no reason to do so), there is still no motivation to select the second compound on page 28 of Bolli et al. (now known as Macitentan) as a lead compound. The compound is not identified by Bolli et al. (or Keyser et al.) as a preferred compound, and Bolli et al. contains no ET_A and ET_B data for the compound, so there is no motivation for those of skill in the art to select Macitentan over any of the over 100 Bolli et al. compounds that do have ET_A and ET_B data.

Indeed, the skilled artisan could have considered, among others, the compounds of Bolli et al. Examples Nos. 18, 20, 23, 24, 29, 100, 109 to 112, 115 to 118, 145, 147, 197, 212 and 214, which all have a high selectivity (and in several cases significantly superior to that of the compound of Example 104 selected by the Examiner), and in any case more than fulfilling the Keyser et al. minimum selectivity criterion of ET_A: ET_B of at least 100 (see paragraph [0049] of Keyser et al.). These are summarized in the table below:

UNITED THERAPEUTICS CORP., EX1006, page 442
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Experimental results for selected compounds as reported in Bolli et al.			
Example No.	IC_{50} for ET_A (nM)	IC_{50} for ET_B (nM)	Selectivity ET_A/ET_B [IC_{50} ET_B/IC_{50} ET_A]
18	8.5	3333	352
20	4.9	1723	351
23	3.6	1585	440
24	2.2	2496	**1134**
29	13.5	4230	313
100	0.76	283	372
104	*0.88*	*601*	*683*
109	1.94	> 1000	> 515
110	2.3	> 1000	> 434
111	12.3	3750	304
112	0.52	257	494
115	2.2	> 1000	> 454
116	1.3	567	436
117	0.45	518	**1151**
118	0.34	611	**1797**
145	1.64	> 1000	**> 609**
147	1.2	408	340
197	1.16	418	360
212	3.1	> 1000	> 322
214	0.76	241	317

UNITED THERAPEUTICS CORP., EX1006, page 443
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

There is no basis in Bolli et al. whatsoever for selecting the compound of Example 104 as lead compound for use in a combination with PDE5 inhibitors such as sildenafil or tadalafil over other compounds that are more selective ET_A antagonists, such as the compounds of Examples 24, 117 or 118 (or rather than a compound with, in the worst case, a possibly slightly lower selectivity, such as the compound of Example 145). Thus, even if the skilled artisan were to start only with the endothelin receptor antagonist compounds of Bolli et al. (and there would be no reason to do so), this would not have led to selection of the lead compound proposed by the Examiner.

Nevertheless, the Examiner defends the selection of Macitentan as a lead compound by arguing, in effect, that motivation exists to choose ***any*** Bolli et al. compound meeting the Keyser et al. definition of a selective ET_A receptor antagonist for combination with a PDE5 inhibitor as taught by Keyser et al. This is clearly erroneous, as it would result in dozens of lead compounds in Bolli alone, as well as those described above in both Keyser et al. and Battistini et al., and completely vitiates the concept of selecting a "lead" by failing to take into account the relative activities of the compounds.

The Examiner attempts to dispose of the fact that Bolli does not report any ET_A and ET_B data for Macitentan by arguing that Bolli et al. discloses that the N-ethyl analog of Macitentan (Example 104 of Bolli) has an activity ratio of about 683, and Macitentan is therefore also expected to have similar activity, because compounds that are homologs "are generally of sufficiently close structural similarity that there is presumed expectation that such compounds possess similar properties." Examiner's Answer at page 14. However, as discussed above and in Appellant's brief, one skilled in the art would not select Example 104 from Bolli et al. as a lead compound out of the universe of ET_A compounds (which extends beyond the Bolli reference) because Keyser et al. does not point to Bolli. Indeed, even if one were to confine that universe to Bolli, its "most preferred" compounds are identified on page 23, and those do not include the compound of Example 104. Further, a preferred ET_A selective antagonist of Keyser et al., sitaxsentan, has a high specificity for ET_A, being 6,500-fold more selective as an antagonist for ET_A compared to ET_B (see Keyser, p. 15, ¶ [058]). Therefore, one skilled in the art would not select Bolli et al. Example 104, which has a much lower selectivity ratio of about 683 to replace sitaxsentan.

UNITED THERAPEUTICS CORP., EX1006, page 444
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

2. Even if Bolli et al. Example 104 was chosen as the lead, there is no motivation to modify the compound to arrive at the compound of formula (I) claimed herein.

Ass discussed above, and in Appellant's brief, selecting the compound of Appellant's claims from Bolli et al. would require choosing it from among the over 200 Bolli examples, without the benefit of any ET_A and ET_B inhibition data, despite the presence in Bolli et al. of 134 compounds that did have ET_A-ET_B binding data. Clearly, such a selection could only be made using impermissible hindsight, with Appellant's disclosure as a guide.

The Examiner argues again that one skilled in the art would expect the activity ratio of Macitentan to be similar to the N-ethyl analog of Example 104, for which ET_A:ET_B selectivity data is disclosed in Bolli et al. Appellant again respectfully disagrees. Biological activities are generally unpredictable and cannot be extrapolated in the abstract as the Examiner did. As discussed in Appellant's brief, even if biological activities could be extrapolated, there are 16 other compounds disclosed on pages 24-28, which are structurally similar to Bolli et al. Example 104. Nothing specifically points to the second compound on page 28 as the preferred compound.

Moreover, as discussed in Appellant's Brief, Keyser et al. specifically ***teaches away*** from using a compound having non-selective ET activity, and particularly compounds having ET_B antagonistic activity. The use of an ET_A-selective antagonist (with little or no antagonistic activity on ET_B) is a fundamental aspect of the Keyser et al. teaching. One skilled in the art would not be motivated to select a compound having ET_B activity (such as the compound of Bolli et al. Example 104, which has ET_B activity) as the lead compound, as there would be no expectation of success. One skilled in the art also would not select Macitentan to be combined with Keyser et al. because if one accepts the Examiner's assumption that the activities of the two compounds would be similar, then Macitentan would be expected to be equally unsuitable.

Accordingly, Appellant respectfully asserts that the Examiner can only select Example 104 as the lead compound and identify motivation to modify to the compound on page 28 of Bolli et al. using hindsight of the current invention. Because there is no legally sufficient motivation to select the currently claimed compound to be used in combination with the teaching of Keyser et al., the present rejection cannot be maintained, and should be withdrawn.

UNITED THERAPEUTICS CORP., EX1006, page 445
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

3. The present invention produces an unexpected effect.

As Appellants have stated, Macitentan (or the compound of formula (I) of the current invention), like Bosentan, is considered by those skilled in the art to be a dual ET_A-ET_B receptor antagonist, has increased potency on the ET_A receptor, and also blocks the ET_B receptor in vivo. Given the explicit disclosure in Keyser et al. of its requirement for ET_A-selective receptor antagonists, and its explicit teaching away from the use of dual ET_A-ET_B receptor antagonists such as Bosentan, one skilled in the art would not have any expectation of success in the use of Macitentan, a dual ET_A/ET_B antagonist, in combination with a PDE5 inhibitor.

Appellant has surprisingly found that the combination of the compound of formula (I), i.e., Macitentan, with a compound having PDE5-inhibitory properties results in an unexpected effect in the treatment of diseases wherein vasoconstriction is involved. Examples 1-3 of the present specification show that in two different rat models, the combination of the PDE5 inhibitor and the compound of Formula I (or Macitentan) provided ABC values that were unexpectedly greater than the sum of the ABC values for administration of either component alone.[1]

The Examiner again dismissed Appellant's assertion of unexpected effect, stating that there was 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." Examiner's Answer at page 14. Appellants respectfully disagree, as the Examiner makes this assertion without any basis whatsoever. As stated above, biological activities are generally unpredictable and cannot be easily extrapolated from one compound to the next. There is no basis for assuming that the unique and unexpected effects discussed in Examples 1-3 of the present specification, and in Appellant's Brief, will also be displayed by the compound of Bolli et al. Example 104, or any other compound. Moreover, as discussed in Appellant's Brief, neither Bolli et al. nor Keyser et al. discloses any unexpected results of the N-ethyl analog in combination with a PDE5 inhibitor, and Keyser et al. does not show any unexpected result at all.

The Examiner failed to consider the unexpected results provided in the application. In view of the preceding remarks, Appellant respectfully asserts that claims 1-11 are not obvious in view of the combination of Bolli et al. and Keyser et al., particularly claims 12-14 where data

[1] ABC = Area Between the control and treatment blood pressure Curves, where a higher value indicates a stronger the effect on lowering blood pressure.

UNITED THERAPEUTICS CORP., EX1006, page 446
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

provided in the specification supports the unobviousness of the combination. Accordingly, the rejection should be withdrawn.

B. Double Patenting Rejections

As discussed in Appellant's Brief, the rejection of claims 1-14 for nonstatutory obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 7,094,781 ("the '781 patent") in view of Bolli et al. and Keyser et al., and the provisional rejection of claims 1-14 for nonstatutory obviousness-type double patenting over claims 1, 9, 10 and 18 of copending U.S. Application Ser. No. 12/388,142 ("the '142 application", now U.S. Patent No. 8,367,685) in view of Bolli et al. and Keyser et al. rely upon the same rationale as the instant rejection under 35 U.S.C. § 103 for alleged obviousness over Bolli et al. in view of Keyser et al. As discussed in detail above, there is no motivation to combine the compound claimed in the '142 application (now the '685 patent) or the '781 patent with a PDE5 inhibitor as Keyser et al. teaches away from this combination. Contrary to the Keyser et al. teaching, the claimed combination possesses unexpected results as there is no reduced efficacy, but in fact enhanced efficacy seen in administering the claimed combination (as discussed in Appellant's Brief). For the reasons stated above, and in Appellant's Brief, these rejections should be withdrawn.

Claims 1-14 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 of the parent case, U.S. Patent No. 8,268,847 ("the '847 patent") in view of Bolli et al. and Keyser et al. The present application is a continuation of the application leading to the '847 patent. Appellant will consider filing a terminal disclaimer over the '847 patent upon an indication of otherwise allowable subject matter in the present application.

CONCLUSION

FOR THESE REASONS, and the reasons discussed in Appellant's Appeal Brief, Appellant respectfully petitions this Honorable Board to reverse the Examiner's rejections of the pending claims for obviousness and obviousness-type double patenting.

UNITED THERAPEUTICS CORP., EX1006, page 447
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

It is believed no additional fee is required. If the fee for entry of this Reply Brief is missing or is insufficient, The Commissioner is authorized to charge the fees necessary for entry of this Appeal Brief to Deposit Account No. 50-4255.

Respectfully Submitted,

Date: August 26, 2014

By: */Michael P. Straher/*

Michael P. Straher
Reg. No. 38,325
Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, NJ 07041
(973) 912-5232

UNITED THERAPEUTICS CORP., EX1006, page 448
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Thomas Hoxie/Stephanie Owusu-Hemeng
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Appeal Forwarding Fee	1413	1	2000	2000
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**2000**

Electronic Acknowledgement Receipt	
EFS ID:	19971293
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Thomas Hoxie/Stephanie Owusu-Hemeng
Filer Authorized By:	Thomas Hoxie
Attorney Docket Number:	AC-66-USC
Receipt Date:	26-AUG-2014
Filing Date:	05-SEP-2012
Time Stamp:	16:55:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2000
RAM confirmation Number	6136
Deposit Account	504255
Authorized User	STRAHER, MICHAEL
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reply Brief Filed	AC-66-USC_Reply_Brief-Final_08262014.pdf	152624 b92d28b6ebc7efdee17c702ebe4a65c21d8e36c7	no	9
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	29908 605e5a2c7f7e34ffb14ff3e2240423429c23e018	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	182532		

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 09/12/2014

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
09/12/2014	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com

United States Patent and Trademark Office

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

Appeal No: 2014-009320
Application: 13/604,148
Appellant: Martine CLOZEL

Patent Trial and Appeal Board Docketing Notice

Application 13/604,148 was received from the Technology Center at the Board on September 02, 2014 and has been assigned Appeal No: 2014-009320.

In all future communications regarding this appeal, please include both the application number and the appeal number.

The mailing address for the Board is:

PATENT TRIAL and APPEAL BOARD
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

Telephone inquiries can be made by calling 571-272-9797 and referencing the appeal number listed above.

By order of the Patent Trial and Appeal Board.

CDC

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/03/2016	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com

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.

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.

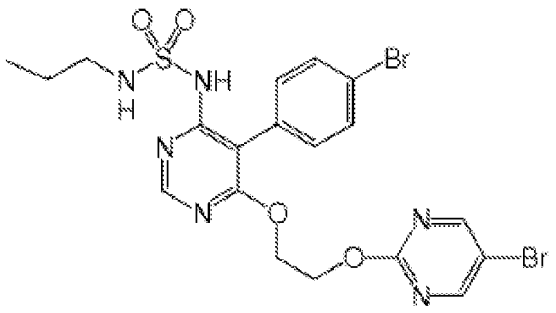
Claim 1 is illustrative of the claims on appeal. Claim 1 provides:

> 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):

---

[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").

UNITED THERAPEUTICS CORP., EX1006, page 457
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847



(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

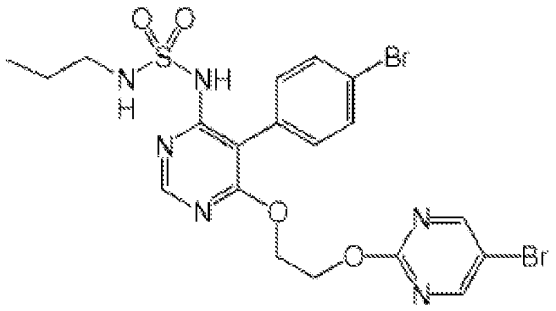
We have reviewed Appellant's arguments in the Briefs, the Examiner's Final Office Action, and the Examiner's Answer to the Appellant's arguments. Although we find that the Examiner made an adequate prima facie case of obviousness, we also find that the Examiner did not adequately respond to Appellant's 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

UNITED THERAPEUTICS CORP., EX1006, page 458
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 459
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 460
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 461
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

> 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)).

UNITED THERAPEUTICS CORP., EX1006, page 462
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 463
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 464
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.

UNITED THERAPEUTICS CORP., EX1006, page 465
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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

UNITED THERAPEUTICS CORP., EX1006, page 466
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

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.").

UNITED THERAPEUTICS CORP., EX1006, page 467
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	13/604,148	Filing Date	2012-09-05	Docket Number (if applicable)	AC-66-USC	Art Unit	1627
First Named Inventor	Martine CLOZEL			Examiner Name	Kendra D CARTER		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 504255

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Michael J. Tsimaras/	Date (YYYY-MM-DD)	2016-12-05
Name	Michael J. Tsimaras	Registration Number	71153

This collection of information is required by 37 CFR 1.114. 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 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.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED THERAPEUTICS CORP., EX1006, page 470
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine CLOZEL
	Art Unit:	1627
	Examiner Name:	Kendra D CARTER
Sheet 1 of 2	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate
		6,458,805	10/01/2002	Blok et al.	
		8,268,847	09/18/2012	Clozel et al.	
		8,541,433	09/24/2013	Clozel et al.	
		9,173,881	11/03/2015	Clozel et al.	
		2013/0317048	11/28/2013	Clozel et al.	
		2013/0310407	11/21/2013	Regenass et al.	
		2014/0148460	05/29/2014	Clozel et al.	
		2014/0329824	11/06/2014	Clozel et al.	

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		JP 2005/0504113	02/10/2005	Novartis AG	
		WO 2003/028730	04/10/2003	Novartis AG	
		WO 2004/056787	07/08/2004	Pfizer Limited	
		WO 2005/112939	12/01/2005	Solvay Pharmaceuticals GMBH	

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
		BARST et al., "Sitaxsentan Therapy for Pulmonary Arterial Hypertension" American Journal of Respiratory and Clinical Care Medicine, (2004), Vol. 169, pg. 441-447.	
		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.	
		BOLLI et al., "The Discovery of N-[5-(4-Bromophenyl)-6-[2-[5-bromo-2-pyrimidinyl)oxy]-4-pyrimidinyl]-N'-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist", Journal of Medicinal Chemistry, dx.doi.org/10.1021/jm30091031, J. Med. Chem. (2012), Vol. 55, pg. 7849-7861.	
		GALIE et al. "Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension", The New England Journal of Medicine, (2005), Vol. 353, pg. 2148-57.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine CLOZEL
	Art Unit:	1627
	Examiner Name:	Kendra D CARTER
Sheet 2 of 2	Attorney Docket No:	AC-66-USC

		GATFIELD et al., "Slow Receptor Dissociation Kinetics Differentiate Macitentan from Other Endothelin Receptor Antagonists in Pulmonary Arterial Smooth Muscle Cells", PLoS ONE, Vol. 7, Issue. 10, e47662 (electronic publication), doi:10.1371/journal.pone.0047662, (Published October 15, 2012), pg. 1-10.	
		Notice of Allowance of U.S Application No. 14/335,657 (Pub No. 2014/0329824)	
		OBERLENDER et al., "Sturctural Variation and (+)- Amphetamine-Like Discriminative Stimulus Properties", (1991), Vol. 38, pg. 581-586.	
		OPITZ et al., "Inhibition of Endothelin Receptors in the Treatment of Pulmonary Arterial Hypertension: Does Selectivity Matter?" European Heart Journal, (2008), Vol. 29, pg. 1936-1948.	
		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.	
		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.	
		Prescribing information of Opsumit® (macitentan), Actelion Pharmaceuticals US, Inc., Issued: October 2013	
		ROARK et al. "Bioisosterism in Drug Design: Identification of the Structure Activity Releationships in a Series of Glycine Anilide ACAT Inhibitors" Bioorganic & Medicinal Chemistry, (1995), Vol. 3(1), pg. 29-39.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL	)	Examiner:	Kendra D CARTER
		)		
Serial No.:	13/604,148	)	Group Art Unit:	1627
		)		
Filed:	September 5, 2012	)	Conf. No.:	5499
		)		
Title:	THERAPEUTIC COMPOSITIONS	)	Docket No.:	AC-66-USC

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicant respectfully requests that this Information Disclosure Statement be entered and the documents listed on the attached form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

The filing of this Information Disclosure Statement is not to be construed as a representation that a search has been made, nor construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability or prior art.

Pursuant to 37 C.F.R. §1.98(a), copies of references which are non US patents and patent applications are enclosed herein.

It is believed that no other fees are due. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), the Commissioner is authorized to charge any additional fees, if needed, or credit any overpayment, to Deposit Account No. 50-4255. If there are any questions, especially ones relating to payments, please contact the undersigned, or if the undersigned is not available, please contact a representative of the firm. Please do not leave voicemails at the undersigned's phone number.

Respectfully submitted,

Date: December 5, 2016

By: /Michael J. Tsimaras/

Michael J. Tsimaras
Reg. No. 71,153

Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, New Jersey 07041
973-912-5232
973-912-5236 (fax)

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Michael John Tsimaras/Glenne Martinez
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 1st Request	1801	1	1200	1200
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt	
EFS ID:	27696019
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Michael John Tsimaras/Glenne Martinez
Filer Authorized By:	Michael John Tsimaras
Attorney Docket Number:	AC-66-USC
Receipt Date:	05-DEC-2016
Filing Date:	05-SEP-2012
Time Stamp:	18:35:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1200
RAM confirmation Number	120616INTEFSW18371700
Deposit Account	504255
Authorized User	Glenne Martinez
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	JP2005504113A.pdf	2201917 26abff591c1fdb6466736765b5487a03b901907f	no	74
Warnings:					
Information:					
2	Foreign Reference	WO03028730A2.pdf	1713158 3444d30076601b56eea59f4bba25a0e5ad083143	no	38
Warnings:					
Information:					
3	Foreign Reference	WO2004056787A1.pdf	4365629 90f169ef6a78afcab2159dbc0bc7ef0c8d15ada0	no	109
Warnings:					
Information:					
4	Foreign Reference	WO2005112939A1.pdf	1515492 5ec89c5c910d10d6b890ee2e4abe963096a64c8f	no	34
Warnings:					
Information:					
5	Non Patent Literature	BARST_2004.pdf	849555 db6469bfc8fb9b2fd66f455352349d691a985e00	no	7
Warnings:					
Information:					
6	Non Patent Literature	Battistini_et_al.pdf	953893 9424d2abc8dc8884f42b666a1d5e584ccb4415de	no	43
Warnings:					
Information:					

7	Non Patent Literature	Bolli_et_al_Discovery_of_an_Orally_Active.pdf	621735 9521f6861e490a02bd14d8794a89b6132b380b73	no	13
Warnings:					
Information:					
8	Non Patent Literature	GALIE_2005.pdf	1237552 814a19e725f10f2d85bf33e80321b7a2188b90c4	no	10
Warnings:					
Information:					
9	Non Patent Literature	Gatfield.pdf	1013740 b001a8134d7cae0ed1c840c5dfa68929428aa2fb	no	11
Warnings:					
Information:					
10	Non Patent Literature	Oberlender_1991.pdf	505070 6dfed6e41ae5c82f8c54d34a87d200616b136ac1	no	6
Warnings:					
Information:					
11	Non Patent Literature	Opitz.pdf	257669 21a8548da3b90389cfb1560cbb4ec291c1245332	no	13
Warnings:					
Information:					
12	Non Patent Literature	OPSUMIT-Full-Prescribing-Information.pdf	99179 5eb74c24f72330a10f2691d71313ca48a5ff9af1	no	6
Warnings:					
Information:					
13	Non Patent Literature	Paul.pdf	99495 2f5de0ea90a5501661ceb76e7c04769793d0ea2a	no	6
Warnings:					
Information:					

14	Non Patent Literature	Pulido.pdf	197095 759b624acb9d00a34457c347854eea7f9979f61e	no	10
Warnings:					
Information:					
15	Request for Continued Examination (RCE)	AC-66-USC_RCE.pdf	1349877 5cc1e0e46d03d7bcaf131795fa3aacaeb80e0697	no	3
Warnings:					
Information:					
16	Non Patent Literature	ROARK_.pdf	807301 501ecc4d2838969ff0da7d4381472a5ef6e5e5e8	no	11
Warnings:					
Information:					
17	Information Disclosure Statement (IDS) Form (SB08)	AC-66-USC_IDS_12052016.pdf	28780 20547e0021dca69781b6343f55d07089a09f977e	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
18	Non Patent Literature	NOA.pdf	414184 41a037aee45f985fa8f87f6238e1b351bba1c773	no	8
Warnings:					
Information:					
19	Transmittal Letter	AC-66-USC_IDS_Transmital_f.pdf	20177 95efe2077126b9fd25b372c842136e193e081a25	no	2
Warnings:					
Information:					
20	Fee Worksheet (SB06)	fee-info.pdf	30322 08e5836ee8eeff80ca55da4e9bb0a7c2a9405cde	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	18281820		

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.

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/26 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional)

In re Application of: Martine CLOZEL

Application No.: 13/604,148

Filed: September 5, 2012

For: THERAPEUTIC COMPOSITIONS

The owner*, ACTELION PHARMACEUTICALS LTD., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8,268,847 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 71,153

/Michael J. Tsimaras/ — December 5, 2016
Signature — Date

Michael J. Tsimaras
Typed or printed name

973-912-5232
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

This collection of information is required by 37 CFR 1.321. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Thomas Hoxie/Glenne Martinez
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	27699066
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Thomas Hoxie/Glenne Martinez
Filer Authorized By:	Thomas Hoxie
Attorney Docket Number:	AC-66-USC
Receipt Date:	05-DEC-2016
Filing Date:	05-SEP-2012
Time Stamp:	19:01:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$160
RAM confirmation Number	120616INTEFSW19024400
Deposit Account	504255
Authorized User	Glenne Martinez
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	AC-66-USC_Terminal_Diclaimer.pdf	373720 f2307339316bae6355e4d808c419624eb18ef022	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30316 2622baef89c8ebd603072ac450e5456a7fd9ce4e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	404036		

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.

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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/604,148	CLOZEL, MARTINE	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 05 December, 2016	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

PAMELA YOUNG

Technology Center: PLRC

Telephone: _____

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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 12/29/2016

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/29/2016	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

HoxiePatentMail@hoxpat.com
HoxiePatentMail@gmail.com

UNITED THERAPEUTICS CORP., EX1006, page 489
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Examiner-Initiated Interview Summary	**Application No.** 13/604,148	**Applicant(s)** CLOZEL, MARTINE	
	Examiner KENDRA D. CARTER	**Art Unit** 1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KENDRA D. CARTER*. (3)_____.

(2) *Michael Tsimaras*. (4)_____.

Date of Interview: *22 December 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-14*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The Examiner asked for an eTD over application 14/162,280 to bring the application to allowance. An office action was requested.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of 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.

☐ Attachment

/KENDRA D CARTER/ Primary Examiner, Art Unit 1627	

UNITED THERAPEUTICS CORP., EX1006, page 490
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Office Action Summary	Application No. 13/604,148	Applicant(s) CLOZEL, MARTINE	
	Examiner KENDRA D. CARTER	Art Unit 1627	AIA (First Inventor to File) Status No

-- 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* MONTHS 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 *5 December 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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) *1-14* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-14* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

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).

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

UNITED THERAPEUTICS CORP., EX1006, page 491
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Patent Trial and Appeal Board, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on December 5, 2016 has been entered.

In light of terminal disclaimer filed over US Patent 8,268,847 and the reversal of all other rejection by the Patent Trial and Appeal Board on October 3, 2016, all previous rejections are withdrawn.

In light of further search a new obviousness-type double patenting rejection is made below.

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 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); *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 nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file

provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-14 are provisionally rejected on the ground of nonstatutory double patenting over claims 1, 10, 15-19, 22, 25 and 28 of copending Application No. 14/162,280 ('280). This is a provisional double patenting rejection because the patentably indistinct claims have not in fact been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: a method of treating hypertension, pulmonary hypertension, or pulmonary arterial hypertension comprising administering a compound of formula (I) and at least one compound having PDE5-

inhibitory properties such as sildenafil, vardenafil, tadalafil and udenafil, wherein the compound of formula I is administered simultaneously, separately or over a period of time not to exceed two or three days.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

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 9:30 am - 6:00 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/
Primary Examiner, Art Unit 1627

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/604,148	CLOZEL, MARTINE	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *KENDRA D. CARTER*. (3)_____.

(2) *Michael Tsimaras*. (4)_____.

Date of Interview: *22 December 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-14*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The Examiner asked for an eTD over application 14/162,280 to bring the application to allowance. An office action was requested.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of 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.

☐ Attachment

/KENDRA D CARTER/ Primary Examiner, Art Unit 1627	

UNITED THERAPEUTICS CORP., EX1006, page 497
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
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 5499

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/604,148	09/05/2012 RULE	514	1627	AC-66-USC

APPLICANTS

INVENTORS

Martine CLOZEL, Binnigen, SWITZERLAND;

**** CONTINUING DATA ***************************

This application is a CON of 12/439,290 02/27/2009 PAT 8268847
which is a 371 of PCT/IB2007/053448 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 ****

09/14/2012

Foreign Priority claimed	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☐	SWITZERLAND	0	14	4
35 USC 119(a-d) conditions met ☑ Yes ☐ No					
Verified and Acknowledged /KENDRA D CARTER/ Examiner's Signature	Initials				

ADDRESS

HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041
UNITED STATES

TITLE

THERAPEUTIC COMPOSITIONS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
1500	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

BIB (Rev. 05/07).

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	Art Unit
	KENDRA D CARTER	1627

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 2300/00, 45/06, 31/4985, 31/506, 31/513	12/22/16	KDC

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (eDAN,PALM)	12/6/12	KDC
STN	12/6/12	KDC
Google (macitentan, PDE5 inhibitor, hypertension, tadalafil, sildenafil)	12/6/12	KDC
Search updated and reviewed	6/4/13	KDC
Inventor search updated	12/22/16	KDC

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	2300/00, 45/06, 31/4985, 31/506, 31/513	12/22/16	KDC

UNITED THERAPEUTICS CORP., EX1006, page 499
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13604148	CLOZEL, MARTINE
	Examiner	**Art Unit**
	KENDRA D CARTER	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/26/2012	06/10/2013	12/22/2016						
	1	✓	✓	✓						
	2	✓	✓	✓						
	3	✓	✓	✓						
	4	✓	✓	✓						
	5	✓	✓	✓						
	6	✓	✓	✓						
	7	✓	✓	✓						
	8	✓	✓	✓						
	9	✓	✓	✓						
	10	✓	✓	✓						
	11	✓	✓	✓						
	12	✓	✓	✓						
	13	✓	✓	✓						
	14	✓	✓	✓						

UNITED THERAPEUTICS CORP., EX1006, page 500
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	33	(PDE5 or sildenafil or tadalafil) and macitentan	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/08/28 15:30
S2	24	(PDE5 or sildenafil or tadalafil) and (ET near antagonist)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/08/28 15:32
S3	2	"20110136818"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/08/28 15:34
S4	2	"20130190336"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2013/08/28 15:34
S5	4	"9173881"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2016/12/22 10:47
S6	3	"13604148"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2016/12/22 11:43
S8	366	hypertension AND (A61K2300/00 OR A61K45/06).cpc. and (A61K31/4985).cpc. and (A61K31/506 OR A61K31/513 OR A61K45/06).CPC.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2016/12/22 12:05
S9	91	S8 and (PDE5 or sildenafil or tadalafil or macitentan)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2016/12/22 12:05
S10	8	("6458805" | "8268847" | "8541433" | "9173881" | "20130317048" | "20130310407" | "20140148460" | "20140329824").PN.	US-PGPUB; USPAT	OR	OFF	2016/12/22 12:11

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S11	291	hypertension AND (A61K2300/00 OR A61K45/06).cpc. and (A61K31/4985).cpc. and (A61K31/506 OR A61K31/513 OR A61K45/06).CPC.	US-PGPUB; USPAT	OR	OFF	2016/12/22 12:08
S12	80	S11 and (PDE5 or sildenafil or tadalafil or macitentan)	US-PGPUB; USPAT	OR	OFF	2016/12/22 12:08

UNITED THERAPEUTICS CORP., EX1006, page 501
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

12/ 22/ 2016 1:59:12 PM
C:\ Users\ kcarter\ Documents\ EAST\ Workspaces\ 13604148.wsp

UNITED THERAPEUTICS CORP., EX1006, page 502
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine CLOZEL
	Art Unit:	1627
	Examiner Name:	Kendra D CARTER
Sheet 1 of 2	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate
		6,458,805	10/01/2002	Blok et al.	
		8,268,847	09/18/2012	Clozel et al.	
		8,541,433	09/24/2013	Clozel et al.	
		9,173,881	11/03/2015	Clozel et al.	
		2013/0317048	11/28/2013	Clozel et al.	
		2013/0310407	11/21/2013	Regenass et al.	
		2014/0148460	05/29/2014	Clozel et al.	
		2014/0329824	11/06/2014	Clozel et al.	

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		~~JP 2005/0504113~~	~~02/10/2005~~	~~Novartis AG~~	
		WO 2003/028730	04/10/2003	Novartis AG	
		WO 2004/056787	07/08/2004	Pfizer Limited	
		WO 2005/112939	12/01/2005	Solvay Pharmaceuticals GMBH	

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	
		BARST et al., "Sitaxsentan Therapy for Pulmonary Arterial Hypertension" American Journal of Respiratory and Clinical Care Medicine, (2004), Vol. 169, pg. 441-447.	
		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.	
		BOLLI et al., "The Discovery of N-[5-(4-Bromophenyl)-6-[2-[5-bromo-2-pyrimidinyl)oxy]-4-pyrimidinyl]-N'-propylsulfamide (Macitentan), an Orally Active, Potent Dual Endothelin Receptor Antagonist", Journal of Medicinal Chemistry, dx.doi.org/10.1021/jm30091031, J. Med. Chem. (2012), Vol. 55, pg. 7849-7861.	
		GALIE et al. "Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension", The New England Journal of Medicine, (2005), Vol. 353, pg. 2148-57.	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.D.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine CLOZEL
	Art Unit:	1627
	Examiner Name:	Kendra D CARTER
Sheet 2 of 2	Attorney Docket No:	AC-66-USC

		GATFIELD et al., "Slow Receptor Dissociation Kinetics Differentiate Macitentan from Other Endothelin Receptor Antagonists in Pulmonary Arterial Smooth Muscle Cells", PLoS ONE, Vol. 7, Issue. 10, e47662 (electronic publication), doi:10.1371/journal.pone.0047662, (Published October 15, 2012), pg. 1-10.	
		Notice of Allowance of U.S Application No. 14/335,657 (Pub No. 2014/0329824)	
		OBERLENDER et al., "Sturctural Variation and (+)- Amphetamine-Like Discriminative Stimulus Properties", (1991), Vol. 38, pg. 581-586.	
		OPITZ et al., "Inhibition of Endothelin Receptors in the Treatment of Pulmonary Arterial Hypertension: Does Selectivity Matter?" European Heart Journal, (2008), Vol. 29, pg. 1936-1948.	
		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.	
		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.	
		Prescribing information of Opsumit® (macitentan), Actelion Pharmaceuticals US, Inc., Issued: October 2013	
		ROARK et al. "Bioisosterism in Drug Design: Identification of the Structure Activity Releationships in a Series of Glycine Anilide ACAT Inhibitors" Bioorganic & Medicinal Chemistry, (1995), Vol. 3(1), pg. 29-39.	

Reference not considered because it was not in English.

EXAMINER /KENDRA D CARTER/ DATE CONSIDERED 12/22/2016

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.D.C/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number:	13/604,148
	Filing Date:	September 5, 2012
	First named Inventor:	Martine CLOZEL
	Art Unit:	1627
	Examiner Name:	Kendra D. CARTER
Sheet 1 of 1	Attorney Docket No:	AC-66-USC

US PATENT DOCUMENTS					
Examiner Initial *	Cite No	Document Number	Publication Date	Name of Patentee or Applicant of Cited Document	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS					
Examiner Initials*	Cite No	Foreign Patent Document	Publication Date	Name of Patentee or Applicant of cited Document	Translation
		EP 0658548	12/15/1994	Tanabe Seiyaku Co., Ltd.	
		EP 0743307	11/20/1996	Tanabe Seiyaku Co., Ltd.	
		JP 2005504113	02/10/2005	Novartis Pharma GMBH	

OTHER DOCUMENTS			
Examiner Initials*	Cite No [1]	Description	

EXAMINER DATE CONSIDERED

* EXAMINER: Please initial if reference considered, draw line through citation if not considered, and include copy of this form with next communication to applicant. 080310

PTO/SB/31 (02-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD

Docket Number (Optional): AC-66-USC

I hereby certify that this correspondence is being facsimile transmitted to the USPTO EFS-Web transmitted to the USPTO, or or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on June 29, 2017

Signature /Glenne Martinez/

Typed or printed name Glenne Martinez

In re Application of: Martine CLOZEL

Application Number	Filed
13/604,148	September 5, 2012

For THERAPEUTIC COMPOSITIONS

Art Unit	Examiner
1627	Kendra D CARTER

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 800.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-4255 .

☐ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

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.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☑ attorney or agent of record. Registration number 71,153.

☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. _____

/Michael J. Tsimaras/
Signature

Michael J. Tsimaras
Typed or printed name

973-912-5232
Telephone number

June 29, 2017
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.31. 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, 1.14 and 41.6. 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	Michael John Tsimaras/Glenne Martinez
Attorney Docket Number:	AC-66-USC

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
NOTICE OF APPEAL	1401	1	800	800
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**2380**

Electronic Acknowledgement Receipt	
EFS ID:	29655597
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	Michael John Tsimaras/Glenne Martinez
Filer Authorized By:	Michael John Tsimaras
Attorney Docket Number:	AC-66-USC
Receipt Date:	29-JUN-2017
Filing Date:	05-SEP-2012
Time Stamp:	18:09:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2380
RAM confirmation Number	063017INTEFSW18102100
Deposit Account	504255
Authorized User	Glenne Martinez
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	AC-66-USC_IDS_Transmittal.pdf	20325 aa46de0316f596e01e497bde80d10ee3f65fe99d	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	AC-66-USC_IDS.pdf	19263 e1f828056973d99aa4543859f92665966845d51b	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	EP_0743307.pdf	2402447 5f7f0e48a6c4c2c992e675e52dbc6915909f9823	no	63
Warnings:					
Information:					
4	Foreign Reference	EP0658548A1.pdf	3291393 263e375c99efd698007c8fc6d6f765f6ffeb9d7d	no	74
Warnings:					
Information:					
5	Foreign Reference	JP2005504113A.pdf	2201917 26abff591c1fdb6466736765b5487a03b901907f	no	74
Warnings:					
Information:					
6	Notice of Appeal Filed	AC-66-USC_Notice_of_Appeal_.pdf	192094 2681f5ef33707ba2f0a99e40315a16bf5f405d71	no	2
Warnings:					

Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	34070 7200890369ae3189912045182aaddba4e8bf8ce7	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	8161509	

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.

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.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Martine CLOZEL et al.	)	Examiner:	Kendra D. CARTER
		)		
Serial No.:	13/604,148	)	Group Art Unit:	1627
		)		
Filed:	September 5, 2012	)	Conf. No.:	5499
		)		
Title:	THERAPEUTIC COMPOSITIONS	)	Docket No.:	AC-66-USC
		)		

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq*., the enclosed materials are brought to the attention of the Examiner for consideration in connection with the above-identified patent application. Applicant respectfully requests that this Information Disclosure Statement be entered and the documents listed on the attached form be considered by the Examiner and made of record. Pursuant to the provisions of MPEP 609, Applicant requests that a copy of the form, initialed as being considered by the Examiner, be returned to the Applicant with the next official communication.

The filing of this Information Disclosure Statement is not to be construed as a representation that a search has been made, nor construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability or prior art.

Pursuant to 37 C.F.R. §1.98(a), copies of references which are non US patents and patent applications are enclosed herein.

INFORMATION DISCLOSURE STATEMENT

Attached is the required fee in the amount of $180.00 in order to have this Information Disclosure Statement considered.Pursuant to 37 C.F.R. §1.97(b), it is believed that no other fees are required with the Information Disclosure Statement. If any other additional fees are presently required, or required during the pendency of this application (other than payment of the issue fee), please charge the same to Deposit Account 50-4255. If there are any questions relating to fee payments associated with this application, please contact the undersigned attorney at the contact information listed below.

Respectfully submitted,

Date: June 29, 2017

By: /Michael J. Tsimaras/
Michael J. Tsimaras/
Reg. No. 71,153

Hoxie & Associates LLC
75 Main Street, Suite 203
Millburn, New Jersey 07041
973-912-5232
973-912-5236 (fax)

PTO/SB/81 (01-09)
Approved for use through 1/31/2010. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	13/604,148
Filing Date	09/05/2012
First Named Inventor	Martine Clozel
Title	Therapeutic Compositions
Art Unit	1627
Examiner Name	Kendra D. Carter
Attorney Docket Number	103893.000594

I hereby revoke all previous powers of attorney given in the above-identified application.

☒ A Power of Attorney is submitted herewith.

OR

☐ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 45511

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐	Firm or Individual Name				
	Address				
	City		State		Zip
	Country				
	Telephone		Email		

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	1/19/2018
Name	Eric Ruhlmann / Thomas Gschwend	Telephone	
Title and Company	Senior Patent Counsel / Deputy Chief Patent Counsel of ACTELION PHARMACEUTICALS LTD		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. 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 3 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Martine Clozel

Application No./Patent No.: 13/604,148 Filed/Issue Date: 09/05/2012

Titled: Therapeutic Compositions

Actelion Pharmaceuticals Ltd , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

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 028901, Frame 0418, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[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.

/David N. Farsiou/ 1/19/2018

Signature Date

David N. Farsiou Reg No. 44104

Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt	
EFS ID:	31549567
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	50446
Filer:	David N. Farsiou/Janis Calvo
Filer Authorized By:	David N. Farsiou
Attorney Docket Number:	AC-66-USC
Receipt Date:	19-JAN-2018
Filing Date:	05-SEP-2012
Time Stamp:	13:14:52
Application Type:	Utility under 35 USC 111(a)

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	Power of Attorney	Power_of_Attorney.PDF	1368075 4fe20b7c836fd08cf7f816e04b4143136dfe1bb8	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	Assignee_Statement_of_Ownership.pdf	69148 5005e37dc8b961020fd3501f94358c6738993c10	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	1437223	

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/604,148	09/05/2012	Martine CLOZEL	103693.000594

CONFIRMATION NO. 5499

45511
Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

POA ACCEPTANCE LETTER

OC000000096859406

Date Mailed: 01/24/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/19/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qtran/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/604,148	09/05/2012	Martine CLOZEL	AC-66-USC

CONFIRMATION NO. 5499

50446
HOXIE & ASSOCIATES LLC
75 MAIN STREET , SUITE 203
MILLBURN, NJ 07041

POWER OF ATTORNEY NOTICE

OC000000096859369

Date Mailed: 01/24/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/19/2018.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qtran/

PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 103693.000594
Application Number 13/604,148	Filed September 5, 2012
For Therapeutic Compositions	
Art Unit 1627	Examiner Kendra D. Carter

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☐	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☑	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$ 3,000.00

☐ 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.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 233050.

☑ Payment made via EFS-Web.

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.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 44,104.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/David N. Farsiou/	January 26, 2018
Signature	Date
David N. Farsiou	215-568-3100
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of one forms are submitted.

This collection of information is required by 37 CFR 1.136(a). 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 6 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: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	13604148
Filing Date:	05-Sep-2012
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Filer:	David N. Farsiou/Marie Duden
Attorney Docket Number:	103693.000594

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 5 months with $0 paid	1255	1	3000	3000
Miscellaneous:				
		Total in USD ($)		**3000**

Electronic Acknowledgement Receipt	
EFS ID:	31619232
Application Number:	13604148
International Application Number:	
Confirmation Number:	5499
Title of Invention:	THERAPEUTIC COMPOSITIONS
First Named Inventor/Applicant Name:	Martine CLOZEL
Customer Number:	45511
Filer:	David N. Farsiou/Marie Duden
Filer Authorized By:	David N. Farsiou
Attorney Docket Number:	103693.000594
Receipt Date:	26-JAN-2018
Filing Date:	05-SEP-2012
Time Stamp:	15:14:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$3000
RAM confirmation Number	012918INTEFSW00001685233050
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	Extension of Time	103693_000594_EOT.PDF	163686 12c121e74c839abe93241c8a8844d8a61aa1d376	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30560 e672e9a44bb920f235ba3a647660f7273b332857	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	194246		

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.

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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/604,148	09/05/2012	Martine CLOZEL	103693.000594	5499

45511 7590 03/22/2018

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PENNSYLVANIA 19104-2891
UNITED STATES OF AMERICA

EXAMINER
CARTER, KENDRA D

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
03/22/2018	ELECTRONIC

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 the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@bakerlaw.com

Notice of Abandonment	**Application No.** 13/604,148	**Applicant(s)** CLOZEL, Martine
	Examiner KENDRA D CARTER	**Art Unit** 1627

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

This application is abandoned in view of:

1. ☑ Applicant's failure to timely file a proper reply to the Office letter mailed on 29 June 2017.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of:(1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☑ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37CFR 1.18 is $ _____ . The publication fee, if required by 37 CFR 1.18(d), is $ _____ .
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

_____

/KENDRA D CARTER/ Primary Examiner, Art Unit 1627	

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

UNITED THERAPEUTICS CORP., EX1006, page 529
UNITED THERAPEUTICS CORP. v. ACTELION PHARMACEUTICALS
U.S. PATENT 8,268,847