

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WJW/FP7358112	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCTUS2017/035867	International filing date (day/month/year) 05.06.2017	Priority date (day/month/year) 06.06.2016	
International Patent Classification (IPC) or national classification and IPC INV. C07D491/107			
Applicant Arena Pharmaceuticals, Inc.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>22</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 04.04.2018		Date of completion of this report 24.05.2018	
Name and mailing address of the international preliminary examining authority:  European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized officer Rufet, Jacques Telephone No. +49 30 25901-332	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2017/035867

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-206 as originally filed

Claims, Numbers

1-47 filed in electronic form on

04-04-2018

Drawings, Figures

1-35 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2017/035867

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 14.05.2018 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-47</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-47</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-47</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

- D1 WO 2006/060122 A2 (ARTESIAN THERAPEUTICS INC [US]; TAYLOR MALCOLM GEORGE [GB]; KLENKE BUR) 8 June 2006
- D2 WO 01/43744 A1 (SANOFI SYNTHELABO [FR]; CECCHI ROBERTO [IT]) 21 June 2001
- D3 WO 99/65895 A1 (SANOFI SYNTHELABO [FR]; CECCHI ROBERTO [IT]; CROCI TIZIANO [IT]; GUZZI) 23 December 1999
- D4 WO 2010/058318 A1 (PFIZER [US]; LONG SCOTT ALLEN [US]; MEYERS MARVIN JAY [US]; PELC MATTH) 27 May 2010

2 Amendments

Claims 1 to 30 and 38 to 47 are based on original claims 1 to 40.

New claims 31 to 34 and 36 are based on original claim 30.

New claims 35 and 37 have a basis in original page 67, lines 4-6 and 35-36 respectively. Thus claims 1 to 47 are acceptable.

2 Method for treatment of the human or animal body by therapy

Claims 41 and 42 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can also dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

3 Novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 47 is considered to be new over the prior art D1 to D4 in the sense of Article 33(2) PCT for the following reasons:

3.1 D1 to D3 refer also to phenoxypropanolamine derivatives as modulators of the beta-3 adrenergic receptor. The structural distinguishing feature of the compounds of present formula (I) over the compounds of D1 to D3 should be seen in the 1-oxa-8-azaspiro[4,5] decane ring system.

3.2 D4 discloses 1-oxa-8-azaspiro[4,5] decane derivatives also useful for treating cardiovascular diseases.

The compounds of D4 do not have the mandatory phenoxypropanolamine skeleton according to present formula (I) nor present variable X.

4 Inventive step

The present application addresses the problem of providing modulators of the beta-3 adrenergic receptor useful for treating or preventing cardiovascular diseases, like heart failure.

4.1 Closest State of the Art and Difference

D1 is considered to represent the closest prior art (CPA), since it refers also to modulators of the beta-3 adrenergic receptor useful for treating or preventing cardiovascular diseases like heart failure having a phenoxypropanolamine skeleton.

The compounds of present claim 1 differs from the compounds of D1 by the nature of the heterocycle (1-oxa-8-azaspiro[4,5] decane ring system) bonded to the amino group of the phenoxypropanolamine skeleton (see D1, claim 1, definition of X).

4.2 Technical effect and objective problem

There is no comparative data in the present application showing that this distinguishing feature is responsible for an unexpected effect over the compounds of D1, thus the objective technical problem solved by the subject-matter of claim 1 should be seen in the provision of a further heterocyclic group in order to provide further modulators of the beta-3 adrenergic receptor.

In view of the examples of table A, the biological data of table B and examples 1 to 4, as well as the figures it is credible that the distinguishing feature solve the abovementioned problem.

4.3 Obviousness of the solution

There is no technical link in D4 as well as D2-D3 which would have incited the skilled worker to replace the heterocycle of the compounds of D1 with the 1-oxa-8-azaspiro[4,5] decane ring system according to present claim 1, if he was looking for alternative modulators of the beta-3 adrenergic receptor having a phenoxypropanolamine skeleton.

The subject-matter of claims 1 to 47 meets thus the requirements of Art. 33(3) PCT.

5 Before the entry into the European phase, claims 43 and 44 should be deleted in accordance with the decision G2/08; the Enlarged Board of Appeal held that the use of Swiss-type claims is permissible in applications having a priority date earlier than 29 January 2011, Art. 54(5) EPC (see G2/08, paragraph 7.1.4 of the reasons for the decision).

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04 April 2018

BY E-FILING

BEFORE THE EUROPEAN PATENT OFFICE (EPO)
ACTING AS THE
INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY (IPEA)

Dear Sirs

International Patent Application No PCT/US2017/035867
Applicant: Arena Pharmaceuticals, Inc.
Our reference: WJW/FP7358112 (240.WO1)

This letter accompanies the Chapter II Demand filed in connection with this application.

Fees

The following fees are being paid with the accompanying letter, which authorises the European Patent Office (EPO) to debit these fees from our deposit account number 2805.0013:

PCT Preliminary Examination Fee	Eur	1830.00
PCT Handling Fee	Eur	175.00
TOTAL:	Eur	<u>2005.00</u>

Enclosures

Filed herewith are:

- (a) replacement pages 207-224 of the claims (claims 1-47) (18 pages).
- (b) "Guide to the Amended Claims filed April 2018" (14 pages).

Amendments

Please cancel all previous claims and substitute new claims 1-47 filed herewith.

The relationship between the new claims and the original claims is shown in the enclosed "Guide".

Briefly:

- new claims 1-30 are identical to original claims 1-30.
- new claims 31-37 have been added; see below.
- new claims 38-47 correspond to original claims 31-40, and have been renumbered accordingly.

Each of new claims 31-37 relates to *one* of the compounds encompassed by at least claim 1:

New Claim No.	Compound	Basis
31	Compound No. 88	See, e.g., original PCT claim 30
32	Compound No. 297	See, e.g., original PCT claim 30
33	Compound No. 309	See, e.g., original PCT claim 30
34	Compound No. 310	See, e.g., original PCT claim 30
35	Compound No. 315	See, e.g., page 67, lines 4-6; and Example 1.68 at page 182, lines 21-23
36	Compound No. 326	See, e.g., original PCT claim 30
37	Compound No. 333	See, e.g., page 67, lines 35-36; and Example 1.42 at pages 135-137

For the avoidance of doubt, it is hereby stated that any subject-matter that is no longer encompassed by the amended claims has not been abandoned. The applicant reserves the right to pursue some or all of such subject-matter in this international application, in one or more corresponding national/regional phase applications, or in one or more continuation or divisional applications thereof.

Cited Documents

The following documents were cited in the ISR:

D1	WO 2006/060122 A2 - Arena Pharmaceuticals, Inc. - 08 June 2006
D2	WO 01/43744 A1 - Sanofi Synthelabo - 21 June 2001
D3	WO 99/65895 A1 - Sanofi Synthelabo - 23 December 1999
D4	WO 2010/058318 A1 - Pfizer - 27 May 2010

Each of the cited documents was published before the priority date of the present application (06 June 2016).

Novelty, Inventiveness, and Industrial Applicability

The Examiner has indicated that all original claims are novel, inventive, and industrially applicable:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement			
1. Statement			
Novelty (N)	Yes: Claims	1-40	
	No: Claims		
Inventive step (IS)	Yes: Claims	1-40	
	No: Claims		
Industrial applicability (IA)	Yes: Claims	1-40	
	No: Claims		

The amended claims are *also* novel, inventive, and industrially applicable.

“Method of Treating or Preventing” Claims

The Examiner has objected to original claims 34 and 35 (corresponding to amended claims 42 and 43), which relate to methods for “*Methods for treating or preventing*”:

1 Method for treatment of the human or animal body by therapy

Claims 34 and 35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can also dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

These claims are maintained at this time, since the Examiner's concerns will not be relevant in all jurisdictions.

“Use in the Manufacture of a Medicament” Claims

The Examiner has objected to original claims 36 and 37 (corresponding to amended claims 43 and 44), which relate to “*Use in the manufacture of a medicament for treating or preventing*”:

4 Before the entry into the European phase, claims 36 and 37 should be deleted in accordance with the decision G2/08; the Enlarged Board of Appeal held that the use of Swiss-type claims is permissible in applications having a priority date earlier than 29 January 2011, Art. 54(5) EPC (see G2/08, paragraph 7.1.4 of the reasons for the decision).

These claims are maintained at this time, since the Examiner's concerns will not be relevant in all jurisdictions.

Closing Remarks

It is requested that an International Preliminary Report on Patentability (IPRP/Chapter II) be issued indicating that all claims are novel, inventive, and industrially applicable.

Yours faithfully

// Wilhelmus J Wytenburg //

Wilhelmus J Wytenburg
APPOINTED AGENT
MEWBURN ELLIS LLP

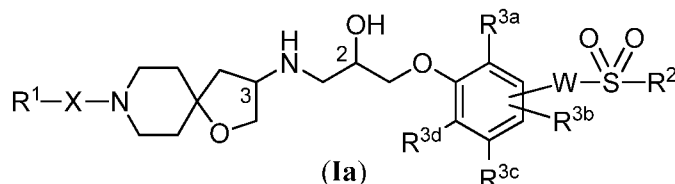
Encs. As above.

WJW/wjw

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CLAIMS

1. A compound selected from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

X is $-\text{SO}_2-$, $-\text{C}(=\text{O})-$, or $-\text{CH}_2\text{C}(=\text{O})-$;

W is absent or C_1 - C_3 alkylene;

R^1 is aryl or heteroaryl, wherein each is optionally substituted with one or more substituents selected from: C_1 - C_6 alkoxy, C_1 - C_6 alkyl, amino, cyano, C_3 - C_7 cycloalkyl, C_1 - C_6 haloalkyl, halogen, hydroxyl, oxo, and sulfamoyl; and wherein said C_1 - C_6 alkyl and C_3 - C_7 cycloalkyl are each optionally substituted with one or more substituents selected from: amino, C_1 - C_6 alkoxy, C_1 - C_6 alkylcarboxamide, $-\text{Y}-\text{C}_3-\text{C}_7$ -cycloalkyl, $-\text{Y}-\text{C}_1-\text{C}_6$ -alkylene-Z, C_1 - C_6 alkylamino, C_1 - C_6 haloalkylamino, and heterocyclyl;

Y is independently selected from: $-\text{O}-$, $-\text{NH}-$, and $-\text{N}-(\text{C}_1-\text{C}_4 \text{ alkyl})-$;

Z is independently selected from: hydroxyl, C_1 - C_6 alkoxy, amino, C_1 - C_6 alkylamino, and C_2 - C_6 dialkylamino;

R^2 is selected from: C_2 - C_6 alkenyl, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, heterocyclyl, and C_1 - C_6 haloalkyl; each optionally substituted with one or more substituents selected from: C_1 - C_6 alkoxy, C_1 - C_6 alkylenehydroxyl, amino, aryl, C_3 - C_7 cycloalkyl, cyano, C_3 - C_7 halocycloalkyl, hydroxyl, and oxo; and

R^{3a} , R^{3b} , R^{3c} , and R^{3d} are each independently H or halogen.

2. The compound according to claim 1, wherein X is $-\text{SO}_2-$.
3. The compound according to claim 1 or 2, wherein W is absent.
4. The compound according to any one of claims 1 to 3, wherein Y is $-\text{NH}-$.
5. The compound according to any one of claims 1 to 4, wherein Z is C_1 - C_6 alkoxy.

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6. The compound according to any one of claims 1 to 5, wherein:
R¹ is aryl optionally substituted with one or more substituents selected from:
C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, halogen,
and sulfamoyl; and wherein said C₁-C₆ alkyl and C₃-C₇ cycloalkyl are each optionally
substituted with one or more substituents selected from: amino,
C₁-C₆ alkylcarboxamide, -NH-C₃-C₇-cycloalkyl, -NH-C₁-C₆-alkylene-NH₂,
-NH-C₁-C₆-alkylene-O-C₁-C₆-alkyl, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, and
heterocyclyl.

7. The compound according to any one of claims 1 to 5, wherein:
R¹ is selected from: 5,6,7,8-tetrahydronaphthalenyl, biphenyl, naphthalenyl,
and phenyl; wherein each is optionally substituted with one or more substituents
selected from:
2-methylpropan-2-yl, bromo, chloro, cyano, cyclopropyl, ethoxy, ethyl, fluoro,
isopropoxy, methoxy, methyl, propan-2-yl, sulfamoyl, and trifluoromethyl; and
wherein said 2-methylpropan-2-yl, cyclopropyl, ethyl, methyl, and propan-2-yl are
each optionally substituted with one or more substituents selected from:
2,2,2-trifluoroethylamino, 2-aminoethylamino, 2-methoxyethylamino,
3-aminopropylamino, acetamido, amino, azetidin-1-yl, butylamino, cyclobutylamino,
ethylamino, isobutylamino, isopropylamino, methylamino, morpholino, propylamino,
tert-butylamino, and *tert*-pentylamino.

8. The compound according to any one of claims 1 to 5, wherein:
R¹ is selected from: 5,6,7,8-tetrahydronaphthalenyl, biphenyl, naphthalenyl,
and phenyl; wherein each is optionally substituted with one or more substituents
selected from:
(2,2,2-trifluoroethylamino)methyl, (2-aminoethylamino)methyl,
(2-methoxyethylamino)methyl, (3-aminopropylamino)methyl, (butylamino)methyl,
(cyclobutylamino)methyl, (ethylamino)methyl, (isobutylamino)methyl,
(isopropylamino)methyl, (methylamino)methyl, (propylamino)methyl,
(*tert*-butylamino)methyl, (*tert*-pentylamino)methyl, 1-amino-2-methylpropan-2-yl,
1-aminocyclopropyl, 2-acetamidoethyl, 2-aminoethyl, 2-aminopropan-2-yl,
aminomethyl, azetidin-1-ylmethyl, bromo, chloro, cyano, ethoxy, fluoro, isopropoxy,
methoxy, methyl, morpholinomethyl, sulfamoyl, and trifluoromethyl.

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9. The compound according to any one of claims 1 to 5, wherein:
 R¹ is selected from: 5,6,7,8-tetrahydronaphthalen-2-yl, biphenyl-3-yl, biphenyl-4-yl, naphthalen-2-yl, and phenyl; wherein each is optionally substituted with one or more substituents selected from:
 (2,2,2-trifluoroethylamino)methyl, (2-aminoethylamino)methyl, (2-methoxyethylamino)methyl, (3-aminopropylamino)methyl, (butylamino)methyl, (cyclobutylamino)methyl, (ethylamino)methyl, (isobutylamino)methyl, (isopropylamino)methyl, (methylamino)methyl, (propylamino)methyl, (*tert*-butylamino)methyl, (*tert*-pentylamino)methyl, 1-amino-2-methylpropan-2-yl, 1-aminocyclopropyl, 2-acetamidoethyl, 2-aminoethyl, 2-aminopropan-2-yl, aminomethyl, azetidin-1-ylmethyl, bromo, chloro, cyano, ethoxy, fluoro, isopropoxy, methoxy, methyl, morpholinomethyl, sulfamoyl, and trifluoromethyl.
10. The compound according to any one of claims 1 to 5, wherein R¹ is selected from:
 1-ethoxynaphthalen-2-yl, 3-(trifluoromethyl)phenyl, 3-bromo-2-methylphenyl, 3-bromo-4-methoxyphenyl, 3-bromophenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 4'-((2,2,2-trifluoroethylamino)methyl)biphenyl-3-yl, 4'-((2-aminoethylamino)methyl)biphenyl-3-yl, 4'-((2-methoxyethylamino)methyl)biphenyl-3-yl, 4'-((3-aminopropylamino)methyl)biphenyl-3-yl, 4'-((butylamino)methyl)biphenyl-3-yl, 4'-((cyclobutylamino)methyl)biphenyl-3-yl, 4'-((ethylamino)methyl)biphenyl-3-yl, 4'-((isobutylamino)methyl)biphenyl-3-yl, 4'-((isopropylamino)methyl)biphenyl-3-yl, 4'-((methylamino)methyl)biphenyl-3-yl, 4'-((propylamino)methyl)biphenyl-3-yl, 4'-((*tert*-butylamino)methyl)biphenyl-3-yl, 4'-((*tert*-pentylamino)methyl)biphenyl-3-yl, 4'-(1-amino-2-methylpropan-2-yl)-4-ethoxybiphenyl-3-yl, 4'-(1-amino-2-methylpropan-2-yl)biphenyl-3-yl, 4'-(1-aminocyclopropyl)-2-methylbiphenyl-3-yl, 4'-(1-aminocyclopropyl)-4-ethoxybiphenyl-3-yl, 4'-(1-aminocyclopropyl)-6-fluorobiphenyl-3-yl, 4'-(1-aminocyclopropyl)-6-methoxybiphenyl-3-yl, 4'-(1-aminocyclopropyl)biphenyl-3-yl, 4'-(2-acetamidoethyl)-4-ethoxy-biphenyl-3-yl, 4'-(2-acetamidoethyl)-biphenyl-3-yl, 4'-(2-aminoethyl)-4-ethoxybiphenyl-3-yl, 4'-(2-aminoethyl)-6-methoxybiphenyl-3-yl, 4'-(2-aminoethyl)biphenyl-3-yl, 4'-(2-aminopropan-2-yl)-4-ethoxybiphenyl-3-yl, 4'-(aminomethyl)-2-methoxybiphenyl-3-yl, 4'-(aminomethyl)-2-methylbiphenyl-3-yl, 4'-(aminomethyl)-3'-fluorobiphenyl-3-yl, 4'-(aminomethyl)-4-ethoxy-3'-fluorobiphenyl-3-yl, 4'-(aminomethyl)-4-ethoxybiphenyl-3-yl, 4'-(aminomethyl)-4-fluorobiphenyl-3-yl, 4'-(aminomethyl)-4-isopropoxybiphenyl-3-yl, 4'-(aminomethyl)-5-methoxybiphenyl-3-yl, 4'-(aminomethyl)-6-ethoxybiphenyl-3-yl, 4'-(aminomethyl)-6-fluorobiphenyl-3-yl, 4'-(aminomethyl)-6-methoxybiphenyl-3-yl,

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4'-(aminomethyl)biphenyl-3-yl, 4'-(aminomethyl)biphenyl-4-yl,
 4'-(azetidin-1-ylmethyl)biphenyl-3-yl, 4'-(morpholinomethyl)biphenyl-3-yl,
 4'-(sulfamoyl)biphenyl-3-yl, 4-bromo-3-methylphenyl,
 4-ethoxy-4'-((isopropylamino)methyl)biphenyl-3-yl, 4'-methylbiphenyl-3-yl,
 5,6,7,8-tetrahydronaphthalen-2-yl, 5-chloronaphthalen-2-yl, 6-chloronaphthalen-2-yl,
 m-tolyl, naphthalen-2-yl, and phenyl.

11. The compound according to any one of claims 1 to 5, wherein R¹ is heteroaryl optionally substituted with one or more substituents selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, amino, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, halogen, hydroxyl, and oxo; and wherein said C₁-C₆ alkyl is optionally substituted with one or more substituents selected from: amino and C₁-C₆ alkoxy.

12. The compound according to any one of claims 1 to 5, wherein R¹ is selected from:
 (1*H*-pyrazolyl)phenyl, (1*H*-pyrazolyl)pyridinyl, (pyridinyl)phenyl,
 (pyrimidinyl)phenyl, 1,2,3,4-tetrahydropyrido[3,2-*b*]pyrazinyl, 1,2-dihydroquinolinyl,
 1,4-dihydroquinolinyl, 1*H*-benzo[*d*]imidazolyl, 1*H*-indazolyl, 1*H*-indolyl,
 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl,
 1*H*-pyrrolo[3,2-*b*]pyridinyl, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridinyl,
 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridinyl, 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazinyl,
 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, 2,3-dihydrobenzofuranyl,
 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridinyl,
 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 3*H*-imidazo[4,5-*b*]pyridinyl,
 (phenyl)pyridinyl, 5,6,7,8-tetrahydroquinolinyl,
 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-3-yl, benzo[*c*][1,2,5]oxadiazolyl, benzofuranyl,
 chromanyl, isoquinolinyl, isoxazolyl, phenylthiophenyl, pyridinyl,
 pyrrolo[1,2-*a*]pyrimidinyl, quinolinyl, and thiazolyl;
 wherein each is optionally substituted with one or more substituents selected from: amino, bromo, chloro, cyclopropyl, ethyl, fluoro, hydroxy, methoxy, methyl, oxo, propan-1-yl, and trifluoromethyl; and wherein said ethyl and methyl are each optionally substituted with one or more substituents selected from: amino and methoxy.

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13. The compound according to any one of claims 1 to 5, wherein R¹ is selected from:
 (1*H*-pyrazolyl)phenyl, (1*H*-pyrazolyl)pyridinyl, (pyridinyl)phenyl,
 (pyrimidinyl)phenyl, 1,2,3,4-tetrahydropyrido[3,2-*b*]pyrazinyl, 1,2-dihydroquinolinyl,
 1,4-dihydroquinolinyl, 1*H*-benzo[d]imidazolyl, 1*H*-indazolyl, 1*H*-indolyl,
 1*H*-pyrazolo[4,3-*b*]pyridinyl, 1*H*-pyrazolyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl,
 1*H*-pyrrolo[3,2-*b*]pyridinyl, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridinyl,
 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridinyl, 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazinyl,
 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, 2,3-dihydrobenzofuranyl,
 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazinyl, 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridinyl,
 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, 3*H*-imidazo[4,5-*b*]pyridinyl,
 (phenyl)pyridinyl, 5,6,7,8-tetrahydroquinolinyl,
 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-3-yl, benzo[*c*][1,2,5]oxadiazolyl, benzofuranyl,
 chromanyl, isoquinolinyl, isoxazolyl, phenylthiophenyl, pyridinyl,
 pyrrolo[1,2-*a*]pyrimidinyl, quinolinyl, and thiazolyl;
 wherein each is optionally substituted with one or more substituents selected
 from: 2-methoxyethyl, amino, aminomethyl, bromo, chloro, cyclopropyl, ethyl, fluoro,
 hydroxy, methoxy, methyl, oxo, propan-1-yl, and trifluoromethyl.
14. The compound according to any one of claims 1 to 5, wherein R¹ is selected from:
 1,2,3,4-tetrahydropyrido[3,2-*b*]pyrazin-7-yl, 1,2-dihydroquinolin-6-yl,
 1,4-dihydroquinolin-3-yl, 1*H*-benzo[d]imidazol-5-yl, 1*H*-indazol-5-yl, 1*H*-indol-2-yl,
 1*H*-indol-3-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl, 1*H*-pyrazol-4-yl,
 1*H*-pyrazolo[4,3-*b*]pyridin-6-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-3-yl,
 1*H*-pyrrolo[3,2-*b*]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl,
 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl,
 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-6-yl,
 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl, 2,3-dihydrobenzofuran-5-yl,
 3-(1*H*-pyrazol-4-yl)phenyl, 3-(pyridin-2-yl)phenyl, 3-(pyridin-3-yl)phenyl,
 3-(pyridin-4-yl)phenyl, 3-(pyrimidin-5-yl)phenyl,
 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl,
 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-6-yl,
 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl, 3*H*-imidazo[4,5-*b*]pyridin-5-yl,
 3*H*-imidazo[4,5-*b*]pyridin-6-yl, 4-(pyridin-2-yl)phenyl, 4-(pyridin-3-yl)phenyl,
 4-(pyridin-4-yl)phenyl, 5-(1*H*-pyrazol-4-yl)pyridin-3-yl, 5-(phenyl)pyridin-3-yl,
 5,6,7,8-tetrahydroquinolin-3-yl, 5-phenylthiophen-2-yl,
 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-3-yl, benzo[*c*][1,2,5]oxadiazol-4-yl,
 benzofuran-2-yl, benzofuran-5-yl, chroman-6-yl, chroman-7-yl, isoquinolin-5-yl,
 isoxazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyrrolo[1,2-*a*]pyrimidin-3-yl, quinolin-3-yl,
 quinolin-6-yl, quinolin-7-yl, and thiazol-4-yl;

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wherein each is optionally substituted with one or more substituents selected from: 2-methoxyethyl, amino, aminomethyl, bromo, chloro, cyclopropyl, ethyl, fluoro, hydroxy, methoxy, methyl, oxo, propan-1-yl, and trifluoromethyl.

15. The compound according to any one of claims 1 to 5, wherein R¹ is selected from:

(*R*)-1,3-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 (*S*)-1,3-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1-(2-methoxyethyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1,3,3-trimethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-6-yl,
 1,4-dimethyl-1,2,3,4-tetrahydropyrido[3,2-*b*]pyrazin-7-yl,
 1,6-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1,8-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1-ethyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1-ethyl-4-oxo-1,4-dihydroquinolin-3-yl, 1-ethyl-5-methyl-1*H*-pyrazol-4-yl,
 1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinolin-3-yl,
 1-ethyl-6-methyl-4-oxo-1,4-dihydroquinolin-3-yl,
 1-ethyl-7-fluoro-4-oxo-1,4-dihydroquinolin-3-yl,
 1-ethyl-7-methyl-4-oxo-1,4-dihydroquinolin-3-yl,
 1-ethyl-8-fluoro-4-oxo-1,4-dihydroquinolin-3-yl,
 1-ethyl-8-methyl-4-oxo-1,4-dihydroquinolin-3-yl, 1*H*-benzo[d]imidazol-5-yl,
 1*H*-indazol-5-yl, 1*H*-indol-2-yl, 1*H*-indol-3-yl, 1*H*-indol-5-yl, 1*H*-indol-6-yl,
 1*H*-pyrazolo[4,3-*b*]pyridin-6-yl, 1*H*-pyrrolo[2,3-*b*]pyridin-3-yl,
 1*H*-pyrrolo[3,2-*b*]pyridin-6-yl, 1-methyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl,
 1-methyl-4-oxo-1,4-dihydroquinolin-3-yl, 2,3-dihydro-[1,4]dioxino[2,3-*b*]pyridin-7-yl,
 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-yl, 2,3-dihydrobenzofuran-5-yl,
 2-aminothiazol-4-yl, 2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-6-yl,
 2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl,
 3-(1-cyclopropyl-1*H*-pyrazol-4-yl)phenyl, 3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl,
 3-(1*H*-pyrazol-4-yl)phenyl, 3-(1-methyl-1*H*-pyrazol-4-yl)phenyl,
 3-(1-propyl-1*H*-pyrazol-4-yl)phenyl, 3-(2-methylpyridin-4-yl)phenyl,
 3-(3-fluoropyridin-2-yl)phenyl, 3-(4-methylpyridin-2-yl)phenyl,
 3-(5-methylpyridin-2-yl)phenyl, 3-(6-(trifluoromethyl)pyridin-2-yl)phenyl,
 3-(6-aminopyridin-3-yl)phenyl, 3-(6-fluoropyridin-2-yl)phenyl,
 3-(6-methylpyridin-2-yl)phenyl, 3-(pyridin-2-yl)phenyl, 3-(pyridin-3-yl)phenyl,
 3-(pyridin-4-yl)phenyl, 3-(pyrimidin-5-yl)phenyl,
 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridin-6-yl, 3,5-dimethylisoxazol-4-yl,
 3-methyl-3*H*-imidazo[4,5-*b*]pyridin-5-yl, 3-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl,
 3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl, 4-(pyridin-2-yl)phenyl,
 4-(pyridin-3-yl)phenyl, 4-(pyridin-4-yl)phenyl, 4-hydroxy-6-methylquinolin-3-yl,
 4-hydroxy-7-methylquinolin-3-yl, 4-hydroxy-8-methylquinolin-3-yl,
 4-hydroxyquinolin-3-yl, 4-methoxyquinolin-3-yl,

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4-methyl-2-oxo-1,2-dihydroquinolin-6-yl,
 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl,
 4-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl,
 4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl, 4-oxo-1,4-dihydroquinolin-3-yl,
 5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl, 5-(4-(aminomethyl)phenyl)pyridin-3-yl,
 5,6,7,8-tetrahydroquinolin-3-yl, 5-bromo-6-chloropyridin-3-yl, 5-bromopyridin-3-yl,
 5-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-3-yl, 5-phenylthiophen-2-yl,
 6-fluoro-4-hydroxyquinolin-3-yl, 7-chlorobenzo[*c*][1,2,5]oxadiazol-4-yl,
 7-fluoro-4-hydroxyquinolin-3-yl, 8-fluoro-4-hydroxyquinolin-3-yl, benzofuran-2-yl,
 benzofuran-5-yl, chroman-6-yl, chroman-7-yl, isoquinolin-5-yl, pyridin-2-yl,
 pyridin-3-yl, pyrrolo[1,2-*a*]pyrimidin-3-yl, quinolin-3-yl, quinolin-6-yl, and quinolin-7-yl.

16. The compound according to any one of claims 1 to 15, R² is selected from:
 1,1-difluoroethyl, 1-fluoroethyl, 2-methylpropan-2-yl, 3,3,3-trifluoropropyl,
 4,4,4-trifluorobutyl, azetidin-3-yl, cyclobutyl, cyclopentyl, cyclopropyl, ethyl,
 fluoromethyl, isobutyl, isopentyl, isopropyl, methyl, oxetan-3-yl, propan-1-yl,
 sec-butyl, and vinyl; each optionally substituted with one or more substituents
 selected from: 2,2-difluorocyclopropyl, amino, cyano, cyclobutyl, cyclohexyl,
 cyclopropyl, ethoxy, hydroxy, hydroxymethyl, methoxy, oxo, and phenyl.
17. The compound according to any one of claims 1 to 15, wherein R² is selected from:
 1-(hydroxymethyl)cyclobutyl, 1-(hydroxymethyl)cyclopropyl,
 1,1-difluoro-2-hydroxyethyl, 1-fluoroethyl, 1-hydroxy-2-methylpropan-2-yl,
 2-amino-2-oxoethyl, 2-hydroxyethyl, 3-amino-3-oxopropyl, 3-hydroxypropyl,
 3-methoxypropyl, cyclobutyl, cyclopropyl, cyclopropylmethyl, ethyl, isobutyl,
 isopropyl, methoxymethyl, methyl, and propan-1-yl.
18. The compound according to any one of claims 1 to 17, wherein R^{3a}, R^{3b}, R^{3c}, and R^{3d}
 are each independently H or F.
19. The compound according to any one of claims 1 to 17, wherein R^{3a}, R^{3b}, R^{3c}, and R^{3d}
 are each H.

- $$\text{Ar}^1\text{--Ar}^2\text{--S(=O)}_2\text{--N} \begin{array}{c} \diagup \text{C}_6\text{H}_{10} \diagdown \\ \diagdown \text{C}_4\text{H}_6 \diagup \end{array} \text{C}_3\text{H}_4\text{N} \begin{array}{c} \text{OH} \\ | \\ \text{CH}_2 \\ | \\ \text{CH}_2\text{O} \end{array} \begin{array}{c} \text{R}^{3a} \\ | \\ \text{C}_6\text{H}_2\text{R}^{3b}\text{R}^{3c}\text{R}^{3d} \\ | \\ \text{SO}_2\text{R}^2 \end{array}$$
- (Ig)

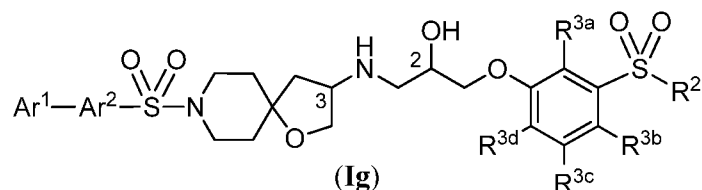
Ar¹ and Ar² are independently 1*H*-pyrazolyl, phenyl, pyridinyl, pyrimidinyl, and thiophenyl, wherein each is optionally substituted with one or more substituents selected from: C₁-C₆ alkoxy, C₁-C₆ alkyl, amino, C₃-C₇ cycloalkyl, C₁-C₆ haloalkyl, halogen, and sulfamoyl; and wherein said C₁-C₆ alkyl and C₃-C₇ cycloalkyl are each optionally substituted with one or more substituents selected from: amino, C₁-C₆ alkylcarboxamide, -NH-C₃-C₇-cycloalkyl, -NH-C₁-C₆-alkylene-NH₂, -NH-C₁-C₆-alkylene-O-C₁-C₆-alkyl, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, and heterocyclyl;

R² is selected from: C₁-C₆ alkyl, C₃-C₇ cycloalkyl, and C₁-C₆ haloalkyl; each optionally substituted with one or more substituents selected from: C₁-C₆ alkoxy, C₁-C₆ alkylenehydroxyl, amino, hydroxyl, and oxo; and

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21. The compound according to claim 1, selected from compounds of Formula (**Ig**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



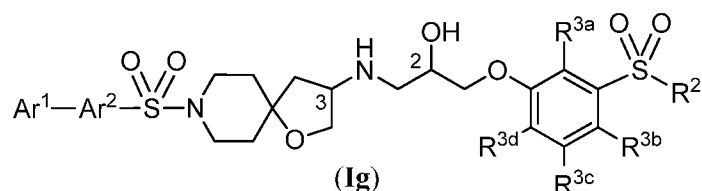
wherein:

Ar¹ and Ar² together form a group selected from: (1*H*-pyrazolyl)phenyl, (1*H*-pyrazolyl)pyridinyl, (phenyl)pyridinyl, (pyridinyl)phenyl, (pyrimidinyl)phenyl, biphenyl, and phenylthiophenyl, wherein each is optionally substituted with one or more substituents selected from: 2-methylpropan-2-yl, amino, cyclopropyl, ethoxy, ethyl, fluoro, isopropoxy, methoxy, methyl, *n*-propyl, propan-2-yl, sulfamoyl, and trifluoromethyl; and wherein said 2-methylpropan-2-yl, cyclopropyl, ethyl, methyl, and propan-2-yl are each optionally substituted with 2,2,2-trifluoroethylamino, 2-aminoethylamino, 2-methoxyethylamino, 3-aminopropylamino, acetamido, amino, azetidin-1-yl, butylamino, cyclobutylamino, ethylamino, isobutylamino, isopropylamino, isopropylamino, methylamino, morpholino, propylamino, *tert*-butylamino, and *tert*-pentylamino;

R² is selected from: 1,1-difluoroethyl, 2-methylpropan-2-yl, cyclopropyl, ethyl, isopropyl, and methyl; each optionally substituted with one or more substituents selected from: amino, hydroxy, hydroxymethyl, methoxy, and oxo; and

R^{3a}, R^{3b}, R^{3c}, and R^{3d} are each H.

22. The compound according to claim 1, selected from compounds of Formula (**Ig**) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

Ar¹ and Ar² together form a group selected from:

3-(1-cyclopropyl-1*H*-pyrazol-4-yl)phenyl, 3-(1-ethyl-1*H*-pyrazol-4-yl)phenyl, 3-(1*H*-pyrazol-4-yl)phenyl, 3-(1-methyl-1*H*-pyrazol-4-yl)phenyl, 3-(1-propyl-1*H*-pyrazol-4-yl)phenyl, 3-(2-methylpyridin-4-yl)phenyl, 3-(3-fluoropyridin-2-yl)phenyl, 3-(4-methylpyridin-2-yl)phenyl, 3-(5-methylpyridin-2-yl)phenyl, 3-(6-(trifluoromethyl)pyridin-2-yl)phenyl, 3-(6-aminopyridin-3-yl)phenyl, 3-(6-fluoropyridin-2-yl)phenyl, 3-(6-methylpyridin-2-yl)phenyl, 3-(pyridin-2-yl)phenyl, 3-(pyridin-3-yl)phenyl, 3-(pyridin-4-yl)phenyl, 3-(pyrimidin-5-yl)phenyl,

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4'-((2,2,2-trifluoroethylamino)methyl)biphenyl-3-yl,
 4'-((2-aminoethylamino)methyl)biphenyl-3-yl,
 4'-((2-methoxyethylamino)methyl)biphenyl-3-yl,
 4'-((3-aminopropylamino)methyl)biphenyl-3-yl, 4'-((butylamino)methyl)biphenyl-3-yl,
 4'-((cyclobutylamino)methyl)biphenyl-3-yl, 4'-((ethylamino)methyl)biphenyl-3-yl,
 4'-((isobutylamino)methyl)biphenyl-3-yl, 4'-((isopropylamino)methyl)biphenyl-3-yl,
 4'-((methylamino)methyl)biphenyl-3-yl, 4'-((propylamino)methyl)biphenyl-3-yl,
 4'-((tert-butylamino)methyl)biphenyl-3-yl, 4'-((tert-pentylamino)methyl)biphenyl-3-yl,
 4'-(1-amino-2-methylpropan-2-yl)-4-ethoxybiphenyl-3-yl,
 4'-(1-amino-2-methylpropan-2-yl)biphenyl-3-yl,
 4'-(1-aminocyclopropyl)-2-methylbiphenyl-3-yl,
 4'-(1-aminocyclopropyl)-4-ethoxybiphenyl-3-yl,
 4'-(1-aminocyclopropyl)-6-fluorobiphenyl-3-yl,
 4'-(1-aminocyclopropyl)-6-methoxybiphenyl-3-yl,
 4'-(1-aminocyclopropyl)biphenyl-3-yl, 4'-(2-acetamidoethyl)-4-ethoxy-biphenyl-3-yl,
 4'-(2-acetamidoethyl)-biphenyl-3-yl, 4'-(2-aminoethyl)-4-ethoxybiphenyl-3-yl,
 4'-(2-aminoethyl)-6-methoxybiphenyl-3-yl, 4'-(2-aminoethyl)biphenyl-3-yl,
 4'-(2-aminopropan-2-yl)-4-ethoxybiphenyl-3-yl,
 4'-(aminomethyl)-2-methoxybiphenyl-3-yl, 4'-(aminomethyl)-2-methylbiphenyl-3-yl,
 4'-(aminomethyl)-3'-fluorobiphenyl-3-yl,
 4'-(aminomethyl)-4-ethoxy-3'-fluorobiphenyl-3-yl,
 4'-(aminomethyl)-4-ethoxybiphenyl-3-yl, 4'-(aminomethyl)-4-fluorobiphenyl-3-yl,
 4'-(aminomethyl)-4-isopropoxybiphenyl-3-yl,
 4'-(aminomethyl)-5-methoxybiphenyl-3-yl, 4'-(aminomethyl)-6-ethoxybiphenyl-3-yl,
 4'-(aminomethyl)-6-fluorobiphenyl-3-yl, 4'-(aminomethyl)-6-methoxybiphenyl-3-yl,
 4'-(aminomethyl)biphenyl-3-yl, 4'-(aminomethyl)biphenyl-4-yl,
 4'-(azetidin-1-ylmethyl)biphenyl-3-yl, 4'-(morpholinomethyl)biphenyl-3-yl,
 4-(pyridin-2-yl)phenyl, 4-(pyridin-3-yl)phenyl, 4-(pyridin-4-yl)phenyl,
 4'-(sulfamoyl)biphenyl-3-yl, 4-ethoxy-4'-((isopropylamino)methyl)biphenyl-3-yl,
 4'-methylbiphenyl-3-yl, 5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl,
 5-(4-(aminomethyl)phenyl)pyridin-3-yl, and 5-phenylthiophen-2-yl;

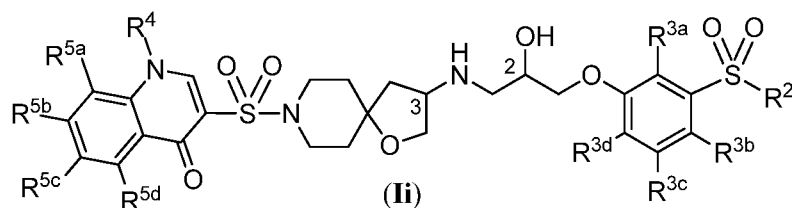
R² is selected from: 1-(hydroxymethyl)cyclopropyl,

1,1-difluoro-2-hydroxyethyl, 1-hydroxy-2-methylpropan-2-yl, 2-amino-2-oxoethyl,
 2-hydroxyethyl, cyclopropyl, ethyl, isopropyl, methoxymethyl, and methyl; and

R^{3a}, R^{3b}, R^{3c}, and R^{3d} are each H.

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23. The compound according to claim 1, selected from compounds of Formula (II) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

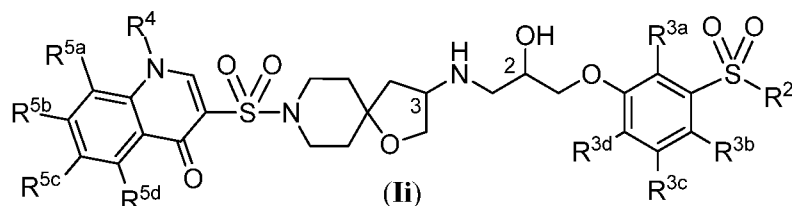
R^2 is selected from: C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, and C_1 - C_6 haloalkyl; each optionally substituted with one or more substituents selected from: C_1 - C_6 alkoxy, C_1 - C_6 alkylenehydroxyl, and hydroxyl;

R^{3a} , R^{3b} , R^{3c} , and R^{3d} are each independently H or halogen;

R^4 is H or C_1 - C_6 alkyl; and

R^{5a} , R^{5b} , R^{5c} , and R^{5d} are independently H, C_1 - C_6 alkyl, and halogen.

24. The compound according to claim 1, selected from compounds of Formula (II) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

R^2 is selected from: 1,1-difluoroethyl, 2-methylpropan-2-yl, cyclopropyl, ethyl, 1-fluoroethyl, isopropyl, and methyl; each optionally substituted with one or more substituents selected from: hydroxy, hydroxymethyl, and methoxy;

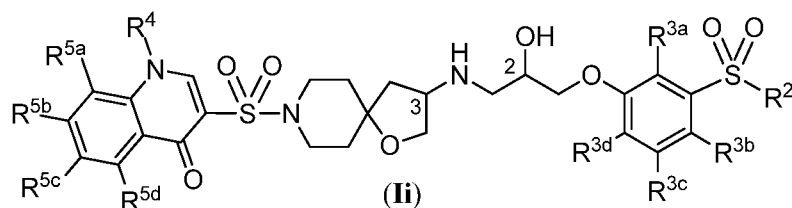
R^{3a} , R^{3b} , R^{3c} , and R^{3d} are each H;

R^4 is selected from: H, methyl, and ethyl; and

R^{5a} , R^{5b} , R^{5c} , and R^{5d} are independently H, methyl, and fluoro.

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25. The compound according to claim 1, selected from compounds of Formula (II) and pharmaceutically acceptable salts, solvates, and hydrates thereof:



wherein:

- R^2 is selected from: 1-(hydroxymethyl)cyclopropyl, 1,1-difluoro-2-hydroxyethyl, 1-fluoroethyl, 1-hydroxy-2-methylpropan-2-yl, cyclopropyl, isopropyl, methoxymethyl, and methyl;
- R^{3a} , R^{3b} , R^{3c} , and R^{3d} are each H;
- R^4 is selected from: H, methyl, and ethyl;
- R^{5a} , R^{5b} , and R^{5c} are independently H, methyl, and fluoro; and R^{5d} is H.
26. The compound according to any one of claims 1 to 25, wherein the stereochemistry for the C(3) carbon of the oxa-azaspiro[4.5]decanyl group bonded to the nitrogen is (*R*) and the stereochemistry for the C(2) carbon of the propyl group bonded to the hydroxyl group is (*S*).
27. The compound according to any one of claims 1 to 25, wherein the stereochemistry for the C(3) carbon of the oxa-azaspiro[4.5]decanyl group bonded to the nitrogen is (*R*) and the stereochemistry for the C(2) carbon of the propyl group bonded to the hydroxyl group is (*R*).
28. The compound according to any one of claims 1 to 25, wherein the stereochemistry for the C(3) carbon of the oxa-azaspiro[4.5]decanyl group bonded to the nitrogen is (*S*) and the stereochemistry for the C(2) carbon of the propyl group bonded to the hydroxyl group is (*S*).
29. The compound according to any one of claims 1 to 25, wherein the stereochemistry for the C(3) carbon of the oxa-azaspiro[4.5]decanyl group bonded to the nitrogen is (*S*) and the stereochemistry for the C(2) carbon of the propyl group bonded to the hydroxyl group is (*R*).
30. The compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, solvates, and hydrates thereof:
 (2*S*)-1-(3-(2-hydroxyethylsulfonyl)phenoxy)-3-(8-(naphthalen-2-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 5**);

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(*S*)-1-(3-(2-hydroxyethylsulfonyl)phenoxy)-3-((*R*)-8-(quinolin-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 88**);

2-(3-((*S*)-2-hydroxy-3-((*R*)-8-(quinolin-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propoxy)phenylsulfonyl)acetamide (**Compound 123**);

(*S*)-1-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)-3-((*R*)-8-(quinolin-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 136**);

(*S*)-1-(3-(cyclopropylsulfonyl)phenoxy)-3-((*R*)-8-(1-methyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazin-7-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 154**);

(*S*)-1-((*R*)-8-(4'-(aminomethyl)-4-ethoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1,1-difluoro-2-hydroxyethylsulfonyl)phenoxy)propan-2-ol (**Compound 161**);

(*S*)-1-((*S*)-8-(4'-(aminomethyl)-4-ethoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 163**);

(*S*)-1-((*R*)-8-(4'-(aminomethyl)-4-fluorobiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 169**);

(*S*)-1-((*R*)-8-(4'-(1-aminocyclopropyl)-6-methoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 199**);

(*S*)-1-((*S*)-8-(4'-(2-aminoethyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1,1-difluoro-2-hydroxyethylsulfonyl)phenoxy)propan-2-ol (**Compound 210**);

(*S*)-1-((*S*)-8-(4'-(2-aminoethyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 211**);

(*S*)-1-((*R*)-8-(4'-(1-aminocyclopropyl)-6-fluorobiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 217**);

(*S*)-1-((*S*)-8-(4'-(aminomethyl)-4-ethoxy-3'-fluorobiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 220**);

(*S*)-1-((*S*)-8-(4'-(1-aminocyclopropyl)-6-methoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 225**);

(*S*)-1-((*S*)-8-(4'-(aminomethyl)-6-methoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 227**);

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(*S*)-1-((*S*)-8-(4'-(aminomethyl)-5-methoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 229**);

(*S*)-1-((*S*)-8-(4'-(aminomethyl)-4-ethoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(methoxymethylsulfonyl)phenoxy)propan-2-ol (**Compound 230**);

(*S*)-1-((*S*)-8-(4'-(aminomethyl)-4-ethoxybiphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(isopropylsulfonyl)phenoxy)propan-2-ol (**Compound 232**);

(2*S*)-1-(3-(1-fluoroethylsulfonyl)phenoxy)-3-((*R*)-8-(quinolin-6-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 234**);

(*S*)-1-((*S*)-8-(4'-((tert-butylamino)methyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 240**);

(*S*)-1-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)-3-((*S*)-8-(4'-((tert-pentylamino)methyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 241**);

(*S*)-1-((*S*)-8-(4'-(azetidin-1-ylmethyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 243**);

(*S*)-1-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)-3-((*S*)-8-(4'-((propylamino)methyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 244**);

(*S*)-1-((*S*)-8-(4'-((butylamino)methyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 245**);

(*S*)-1-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)-3-((*S*)-8-(4'-((2-methoxyethylamino)methyl)biphenyl-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 247**);

3-((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-1-ethylquinolin-4(1*H*)-one (**Compound 297**);

(*S*)-1-(3-(1-(hydroxymethyl)cyclopropylsulfonyl)phenoxy)-3-((*R*)-8-(naphthalen-2-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 300**);

(*S*)-1-((*R*)-8-(1*H*-pyrrolo[3,2-*b*]pyridin-6-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 309**);

1-ethyl-3-((*R*)-3-((*S*)-2-hydroxy-3-(3-(methylsulfonyl)phenoxy)propylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 310**);

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(*S*)-1-((*R*)-8-(1*H*-pyrrolo[3,2-*b*]pyridin-6-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(methylsulfonyl)phenoxy)propan-2-ol (**Compound 320**);

(*S*)-1-((*R*)-8-(1*H*-pyrrolo[3,2-*b*]pyridin-6-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(isopropylsulfonyl)phenoxy)propan-2-ol (**Compound 321**);

1-ethyl-8-fluoro-3-((*R*)-3-((*S*)-2-hydroxy-3-(3-(methylsulfonyl)phenoxy)propylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 322**);

3-((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 326**);

3-((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-8-methylquinolin-4-ol (**Compound 327**);

3-((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-7-fluoroquinolin-4-ol (**Compound 329**); and

1-ethyl-8-fluoro-3-((*R*)-3-((*S*)-2-hydroxy-3-(3-(isopropylsulfonyl)phenoxy)propylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 331**).

31. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

(*S*)-1-(3-(2-hydroxyethylsulfonyl)phenoxy)-3-((*R*)-8-(quinolin-3-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)propan-2-ol (**Compound 88**).

32. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

3-((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-1-ethylquinolin-4(1*H*)-one (**Compound 297**).

33. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

(*S*)-1-((*R*)-8-(1*H*-pyrrolo[3,2-*b*]pyridin-6-ylsulfonyl)-1-oxa-8-azaspiro[4.5]decan-3-ylamino)-3-(3-(cyclopropylsulfonyl)phenoxy)propan-2-ol (**Compound 309**).

34. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:

1-ethyl-3-((*R*)-3-((*S*)-2-hydroxy-3-(3-(methylsulfonyl)phenoxy)propylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 310**).

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35. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:
3-(((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-1-ethyl-8-methylquinolin-4(1*H*)-one (**Compound 315**).
36. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:
3-(((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)quinolin-4(1*H*)-one (**Compound 326**).
37. The compound according to claim 1, selected from the following compound and pharmaceutically acceptable salts, solvates, and hydrates thereof:
3-(((*R*)-3-((*S*)-3-(3-(cyclopropylsulfonyl)phenoxy)-2-hydroxypropylamino)-1-oxa-8-azaspiro[4.5]decan-8-ylsulfonyl)-1-ethyl-8-fluoroquinolin-4(1*H*)-one (**Compound 333**).
38. A pharmaceutical product selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a compound according to any one of claims 1 to 37.
39. A pharmaceutical composition comprising a compound according to any one of claims 1 to 37, and a pharmaceutically acceptable carrier.
40. A method for preparing a pharmaceutical composition comprising the step of admixing a compound according to any one of claims 1 to 37, and a pharmaceutically acceptable carrier.
41. A method for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of
 - a compound according to any one of claims 1 to 37;
 - a pharmaceutical product according to claim 38; or
 - a pharmaceutical composition according to claim 39.

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42. A method for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of
- a compound according to any one of claims 1 to 37;
 - a pharmaceutical product according to claim 38; or
 - a pharmaceutical composition according to claim 39;
- wherein said beta-3 adrenergic receptor-mediated disorder is selected from the list consisting of:
- heart failure; cardiac performance in heart failure; mortality, reinfarction, and/or hospitalization in connection with heart failure; acute heart failure; acute decompensated heart failure; congestive heart failure; severe congestive heart failure; organ damage associated with heart failure (*e.g.*, kidney damage or failure, heart valve problems, heart rhythm problems, and/or liver damage); heart failure due to left ventricular dysfunction; heart failure with normal ejection fraction; cardiovascular mortality following myocardial infarction; cardiovascular mortality in patients with left ventricular failure or left ventricular dysfunction; left ventricular failure; left ventricular dysfunction; class II heart failure using the New York Heart Association (NYHA) classification system; class III heart failure using the New York Heart Association (NYHA) classification system; class IV heart failure using the New York Heart Association (NYHA) classification system; LVEF < 40% by radionuclide ventriculography; and LVEF $\leq$ 35% by echocardiography or ventricular contrast angiography.
43. Use of a compound according to any one of claims 1 to 37 in the manufacture of a medicament for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual.
44. Use of a compound according to any one of claims 1 to 37 in the manufacture of a medicament for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual, wherein said beta-3 adrenergic receptor-mediated disorder is selected from the list consisting of:
- heart failure; cardiac performance in heart failure; mortality, reinfarction, and/or hospitalization in connection with heart failure; acute heart failure; acute decompensated heart failure; congestive heart failure; severe congestive heart failure; organ damage associated with heart failure (*e.g.*, kidney damage or failure, heart valve problems, heart rhythm problems, and/or liver damage); heart failure due to left ventricular dysfunction; heart failure with normal ejection fraction; cardiovascular mortality following myocardial infarction; cardiovascular mortality in patients with left ventricular failure or left ventricular dysfunction; following myocardial infarction; left ventricular failure; left ventricular dysfunction; class II heart failure using the New York Heart Association (NYHA) classification system; class III heart

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failure using the New York Heart Association (NYHA) classification system; class IV heart failure using the New York Heart Association (NYHA) classification system; LVEF < 40% by radionuclide ventriculography; and LVEF $\leq$ 35% by echocardiography or ventricular contrast angiography.

45. A compound according to any one of claims 1 to 37;
a pharmaceutical product according to claim 38; or
a pharmaceutical composition according to claim 39;
for use in a method of treatment of the human or animal body by therapy.
46. A compound according to any one of claims 1 to 37;
a pharmaceutical product according to claim 38; or
a pharmaceutical composition according to claim 39;
for use in a method for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual.
47. A compound according to any one of claims 1 to 37;
a pharmaceutical product according to claim 38; or
a pharmaceutical composition according to claim 39;
for use in a method for treating or preventing a beta-3 adrenergic receptor-mediated disorder in an individual, wherein said beta-3 adrenergic receptor-mediated disorder is selected from the list consisting of:
heart failure; cardiac performance in heart failure; mortality, reinfarction, and/or hospitalization in connection with heart failure; acute heart failure; acute decompensated heart failure; congestive heart failure; severe congestive heart failure; organ damage associated with heart failure (e.g., kidney damage or failure, heart valve problems, heart rhythm problems, liver damage); heart failure due to left ventricular dysfunction; heart failure with normal ejection fraction; cardiovascular mortality following myocardial infarction; cardiovascular mortality in patients with left ventricular failure or left ventricular dysfunction; left ventricular failure; left ventricular dysfunction; class II heart failure using the New York Heart Association (NYHA) classification system; class III heart failure using the New York Heart Association (NYHA) classification system; class IV heart failure using the New York Heart Association (NYHA) classification system; LVEF < 40% by radionuclide ventriculography; and LVEF $\leq$ 35% by echocardiography or ventricular contrast angiography.