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Date

15.07.16

Reference 55829-EP-EPT02	Application No./Patent No. 14803001.8 - 1452
Applicant/Proprietor NOVARTIS AG	

Communication pursuant to Rules 161(1) and 162 EPC

1. Comments on the written opinion and amendment of the application (R. 161(1) EPC)

The above-mentioned international (Euro-PCT) application has entered the European phase.

The EPO as International Searching Authority and, where a demand under Article 31 PCT was filed, also as International Preliminary Examining Authority has drawn up a written opinion on this application or the EPO as Supplementary International Searching Authority has issued explanations pursuant to Rule 45bis.7(e) PCT to the supplementary international search report.

In accordance with Rule 161(1) EPC, you may comment on the written opinion or on the explanations to the supplementary international search report within a **non-extendable period of six months** after notification of the present communication.

Under Articles 28, 41 PCT and Rules 52, 78 PCT the application may be amended before a designated or elected Office, and in accordance with Rule 137(2) EPC the applicant may amend the description, claims and drawings of his own volition together with any comments, corrections or amendments made in response to the communication under Rule 161(1) EPC.

Whether or not you have already done so, you now have a further opportunity to file amended claims or other application documents within the above-mentioned period.

Please note that under Rule 137(2) and (3) EPC as in force from 1 April 2010, you may amend the description, claims and drawings of your own volition in response to this communication, if the international search report has been drawn up on or after 1 April 2010 or the EPO has issued a supplementary international search report. In these cases no further amendments may be made without the consent of the Examining Division. This may be in particular relevant if you have already filed comments/amendments with respect to a written opinion of the International Searching Authority or an international preliminary examination report, or to any explanations pursuant to Rule 45bis.7(e) PCT to the supplementary international search report, which however do not address the deficiencies noted therein and you choose not to react to the present communication.

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

The claims applicable on expiry of this period, i.e. those filed on entry into the European phase or in response to the present communication, will form the basis for the calculation of any claims fee to be paid (see p. 2).

2. Claims fees under Rule 162 EPC

If the application documents on which the European grant procedure is to be based comprise more than fifteen claims, a claims fee shall be payable for the sixteenth and each subsequent claim within the period provided for in Rule 159(1) EPC.

- ☐ Based on the application documents currently on file, all necessary claims fees have already been paid (or the documents do not comprise more than 15 claims).
- ☒ All necessary fees will be debited automatically according to the automatic debit order.
- ☐ The claims fees due for the claims to were not paid within the above-mentioned period.

Any outstanding claims fee, either based on the current set of claims or on any amended claims to be filed pursuant to Rule 161 EPC (see page 1), may still be validly paid within a **non-extendable period of six months** after notification of this communication (R. 162(2) EPC).

If a payment is made for only some of the claims, you must indicate for which claims it is intended. If a claims fee is not paid in due time, the claim concerned is deemed to be abandoned (R. 162(4) EPC).

If claims fees have already been paid, but on expiry of the above-mentioned period there is a new set of claims containing fewer fee-incurring claims than before, the claims fees in excess of those due under Rule 162(2), second sentence EPC will be refunded (R. 162(3) EPC).

The claims fee is currently

EUR 235 for the 16th and each subsequent claim up to the limit of 50
EUR 585 for the 51st and each subsequent claim

Note to users of the automatic debiting procedure

Unless the EPO receives prior instructions to the contrary, the fees for all claims incurring fees will be debited on the last day of the period for payment. For further details see the Arrangements for the automatic debiting procedure, Annex A.1 to the ADA, Point 6.1(d), supplementary publication 3 - OJ EPO 2015.

Important information concerning fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

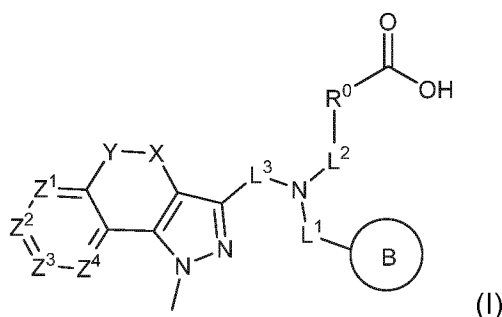
Payments by cheque delivered or sent direct to the EPO are no longer accepted as from 1 April 2008 (see OJ EPO 2007, 626).

For the Examining Division



CLAIMS

1. A compound according to formula (I),



or a pharmaceutical acceptable salt thereof, wherein,

5 R^0 is Ring A or C_{1-6} alkyl;

Ring A is aryl; 5-10 membered heteroaryl comprising 1-3 N, O or S heteroatoms; or C_{3-7} cycloalkyl; and said Ring A is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

10 Ring B is aryl; 5-10 membered heteroaryl comprising 1-3 N, O or S heteroatoms; or C_{3-7} cycloalkyl; and said Ring B is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

X is $-(CR^4R^5)-$;

Y is $-O-$, $-(CR^4R^5)-$, or $*-O(CR^4R^5)-$, wherein "*" indicates the point of attachment of Y to the ring containing the Z ring atoms;

15 Z^1 , Z^2 , Z^3 , and Z^4 are each independently $-CR^3-$ or $-N-$;

L^1 is $*^1-(CR^4R^5)_{1,2}-$ wherein $*^1$ indicates the point of attachment of L^1 to N;

L^2 is $*^2-(CR^4R^5)_{1,2}-$, $*^2-(CR^4R^5)-C(O)-NR-$, $*^2-(CR^4R^5)_2-O-$, $*^2-(CR^4R^5)_2-NR-$ or $*^2-(CR^4R^5)-C(O)-NR-(CR^4R^5)-$; wherein $*^2$ indicates the point of attachment of L^2 to N;

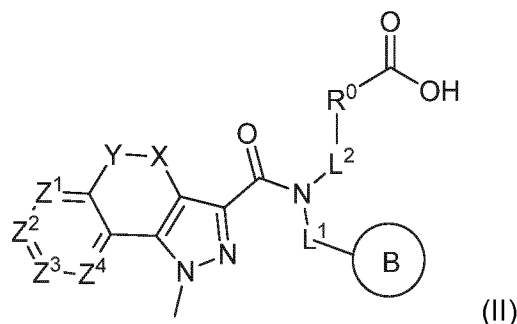
L^3 is $-C(O)-$;

20 each R^2 is independently halo, C_{1-6} alkyl, or halo-substituted C_{1-6} alkyl;

each R^3 is independently hydrogen, halo, or C_{1-6} alkyl;

R , R^4 and R^5 are independently hydrogen or C_{1-6} alkyl.

2. The compound according to claim 1, wherein the compound is of Formula (II):



or a pharmaceutically acceptable salt thereof; wherein,

R^0 is Ring A or C_{1-6} alkyl; wherein Ring A is phenyl, pyridyl or cyclopropyl, each of which is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

Ring B is selected from phenyl, pyridyl, 1*H*-indolyl, and C_{3-7} cycloalkyl, each of which is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

X is $-(CR^4R^5)-$;

Y is $-O-$, $-(CR^4R^5)-$ or $*-O(CR^4R^5)-$, wherein “*” indicates the point of attachment of Y to the ring containing the Z ring atoms;

Z^1 , Z^2 , Z^3 , and Z^4 are each independently $-CR^3-$ or $-N-$;

L^1 is $*^1-(CR^4R^5)_{1-2}-$ wherein “*1” indicates the point of attachment of L^1 to N;

L^2 is $*^2-(CR^4R^5)_{1-2}-$, $*^2-(CR^4R^5)-C(O)-NR-$, $*^2-(CR^4R^5)_2-O-$, $*^2-(CR^4R^5)_2-NR-$ or $*^2-(CR^4R^5)-C(O)-NR-(CR^4R^5)-$; where “*2” indicates the point of attachment of L^2 to N;

each R^2 is independently halo, C_{1-6} alkyl, or halo-substituted C_{1-6} alkyl;

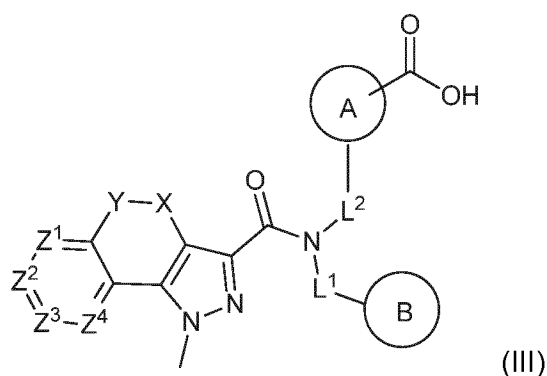
each R^3 is independently hydrogen, halo, or C_{1-6} alkyl; and

R , R^4 and R^5 are independently hydrogen or C_{1-6} alkyl.

3. The compound according to claim 1 or 2, wherein R^0 is selected from

$*^3-CH_2C(CH_3)_2-$, $*^3-CH_2CH(CH_3)-$, and $*^3-cyclopropane-1,1,-diyl$, wherein “*3” indicates the point of attachment of R^0 to L^2 .

4. The compound according to claim 1 or 2, wherein the compound is of Formula (III):



or a pharmaceutically acceptable salt thereof; wherein

Ring A is phenyl or pyridyl, each of which is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

Ring B is selected from phenyl, pyridyl, 1*H*-indolyl, and cyclopentyl, each of which is unsubstituted or substituted by 1-2 substituents independently represented by R^2 ;

L^1 is $-(CR^4R^5)-$;

L^2 is selected from $-(CH_2)-$, $^{*2}-CH_2C(O)NH-$, $^{*2}-CH(CH_3)C(O)NH-$, $^{*2}-CH_2C(O)NHCH_2-$, $^{*2}-(CH_2)_2O-$, and $^{*2}-(CH_2)_2NH-$; wherein “ ^{*2} ” indicates the point of attachment of L^2 to N;

X is CH_2 ;

Y is selected from $-O-$, $-CH_2-$, $-C(CH_3)_2-$ and $^{*}-O-CH_2-$, wherein “ * ” indicates the point of attachment of Y to the ring containing the Z ring atoms;

Z^1 is CR^3 or N;

Z^2 is CR^3 ;

Z^3 is CR^3 ;

Z^4 is CR^3 or N;

each R^2 is independently selected from halo, methyl, and trifluoromethyl;

each R^3 is independently hydrogen, halo, or C_{1-6} alkyl; and

each of R^4 and R^5 is independently hydrogen or methyl.

5. The compound according to any one of claims 1 to 4, wherein L^2 is selected from $-(CH_2)-$, $^{*2}-CH_2C(O)NH-$, $^{*2}-(CH_2)_2O-$, and $^{*2}-(CH_2)_2NH-$; wherein “ ^{*2} ” indicates the point of attachment of L^2 to N;

6. The compound according to any one of claim 1 to 5, wherein each R^2 is independently fluoro or methyl.

7. The compound according to any one of claim 1 to 6, wherein each R^3 is independently selected from hydrogen, fluoro, chloro, and methyl.

8. The compound according to any one of claims 1 to 7, wherein

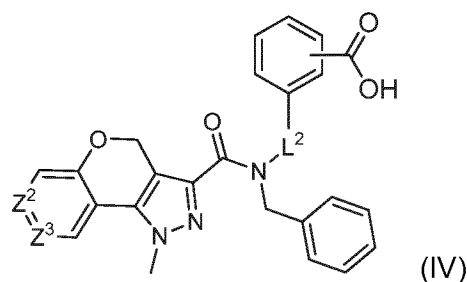
Z^1 is selected from CH, CF, CCH_3 , and N;

Z^2 is selected from CH, CF, CCl, and CCH_3 ;

Z^3 is selected from CH, CF, CCl, and CCH_3 ; and

Z^4 is CH or N.

9. The compound of claim 1, wherein said compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof; wherein

each phenyl ring is optionally further substituted by 1-2 substituents independently represented by R^2 , wherein R^2 is fluoro or methyl;

5 L^2 is selected from $-CH_2-$, $^{*2}-CH_2CH_2NH-$, $^{*2}-CH_2CH_2O-$, and $^{*2}-CH_2C(O)NH-$, wherein ^{*2} indicates the point of attachment of L^2 to N;

Z^2 is selected from CH, CF, CCl, and CCH_3 ; and

Z^3 is selected from CH, CF, CCl, and CCH_3 .

10. The compound according to claim 1 selected from:

10 4-fluoro-3-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

15 3-(2-(8-chloro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

4-fluoro-3-(2-(1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(N-(2-fluorobenzyl)-1,8-dimethyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

20 3-(2-(N-(2-fluorobenzyl)-1,6-dimethyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

25 3-(2-(7-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(7-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(6,8-difluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

5 3-(2-(8-chloro-N-(2-fluorobenzyl)-1,7-dimethyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1,6-dimethyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

10 3-(2-(8-chloro-6-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(7,8-difluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

15 3-(2-(7,8-difluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(N-benzyl-7,8-difluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

20 4-fluoro-3-(2-(8-fluoro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(N-(2-fluorobenzyl)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinoline-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(N-(2-fluorobenzyl)-1-methyl-4,5-dihydro-1H-pyrazolo[3,4-f]quinoline-3-carboxamido)acetamido)benzoic acid;

25 (S)-4-fluoro-3-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)propanamido)benzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamido)acetamido)benzoic acid;

30 3-(2-(8-chloro-7-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(N-(3-fluorobenzyl)-1,5,5-trimethyl-4,5-dihydro-1H-benzo[g]indazole-3-carboxamido)acetamido)benzoic acid;

4-fluoro-3-(2-(N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

35 3-(2-(8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

5 3-(2-(N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(N-benzyl-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

10 3-(2-(N-benzyl-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(9-chloro-N-(2-fluorobenzyl)-1-methyl-4,5-dihydro-1H-benzo[2,3]oxepino[4,5-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

15 3-(2-(8-chloro-N-(cyclopentylmethyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-(2-(8-chloro-N-(cyclopentylmethyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

20 3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-5-fluorobenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-methylbenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-2-methylpropanoic acid;

25 3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-2,2-dimethylpropanoic acid;

1-((2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)methyl)cyclopropanecarboxylic acid;

30 4-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

4-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

35 N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-methylbenzoic acid;

4-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3,5-dimethylbenzoic acid;

3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-4-fluorobenzoic acid;

5 4-(2-(8-chloro-N-(cyclopentylmethyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3,5-dimethylbenzoic acid;

4-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3,5-difluorobenzoic acid;

10 4-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-(trifluoromethyl)benzoic acid;

4-(2-(N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3,5-difluorobenzoic acid;

3,5-difluoro-4-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

15 4-(2-(N-benzyl-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3,5-difluorobenzoic acid;

4-(2-(N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

20 4-(2-(N-benzyl-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

4-(2-(N-benzyl-7,8-difluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

3-fluoro-4-(2-(8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

25 4-(2-(7,8-difluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

4-(2-(8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

30 3-fluoro-4-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

4-(2-(7,8-difluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)-3-fluorobenzoic acid;

3-((2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

35 3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

3-((2-(8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

3-((2-(8-chloro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

5 4-fluoro-3-((2-(8-fluoro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

3-((2-(7,8-difluoro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

10 4-fluoro-3-((2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

4-fluoro-3-((2-(N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

3-((2-(N-benzyl-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

15 3-((2-(N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

3-((2-(7,8-difluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

20 3-((2-(N-benzyl-7,8-difluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

4-((N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-3-fluorobenzoic acid;

25 4-((8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-N-(3,5-difluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

30 4-((N-benzyl-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-3-fluorobenzoic acid;

4-((8-chloro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-N-(2,3-difluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

35 4-((8-chloro-N-(3-fluoro-5-methylbenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((N-(3,5-difluorobenzyl)-8-fluoro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-3-fluorobenzoic acid;

5 3-fluoro-4-((8-fluoro-1-methyl-N-(3-methylbenzyl)-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((N-((1H-indol-5-yl)methyl)-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

10 5-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)picolinic acid;

4-((8-chloro-N-((5-fluoropyridin-3-yl)methyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-N-((5-chloropyridin-3-yl)methyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

15 4-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-2-fluorobenzoic acid;

4-((N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-2-fluorobenzoic acid;

20 N-benzyl-N-(4-carbamoylbenzyl)-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamide;

4-((8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-3-fluorobenzoic acid;

25 3-fluoro-4-((8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

4-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid ;

30 4-((8-chloro-N -(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-3-fluorobenzoic acid

4-((8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-2-fluorobenzoic acid;

6-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)nicotinic acid;

35 5-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)-6-methylpicolinic acid;

4-fluoro-3-((2-(8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid; and

3-((2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

5 or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1 selected from:

4-fluoro-3-(2-(8-fluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

10 4-fluoro-3-(2-(8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(7-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)benzoic acid;

3-(2-(7,8-difluoro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)acetamido)-4-fluorobenzoic acid;

15 3-(2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethoxy)benzoic acid;

3-((2-(8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

20 3-((2-(8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)-4-fluorobenzoic acid;

4-((N-benzyl-8-chloro-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

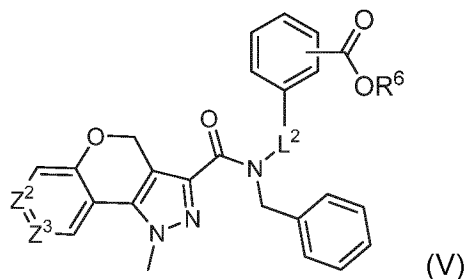
4-((8-chloro-N-(2-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid;

25 4-((8-chloro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)methyl)benzoic acid; and

4-fluoro-3-((2-(8-fluoro-N-(3-fluorobenzyl)-1-methyl-1,4-dihydrochromeno[4,3-c]pyrazole-3-carboxamido)ethyl)amino)benzoic acid;

or a pharmaceutically acceptable salt thereof.

30 12. A compound of Formula (V)



wherein each phenyl ring is optionally further substituted by 1-2 substituents independently represented by R^2 , wherein R^2 is fluoro or methyl;

5 L^2 is selected from $-CH_2-$, $^{*2}-CH_2CH_2NH-$, $^{*2}-CH_2CH_2O-$, and $^{*2}-CH_2C(O)NH-$, wherein “ ^{*2} ” indicates the point of attachment of L^2 to N;

Z^2 is selected from CH, CF, CCl, and CCH_3 ;

Z^3 is selected from CH, CF, CCl, and CCH_3 ; and

R^6 is C_{1-6} alkyl.

10

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-11 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15 14. A combination comprising a therapeutically effective amount of a compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, and a second therapeutic agent.

15. A compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, for use in treating a condition mediated by FXR, wherein said condition mediated by FXR is a liver disease selected from intrahepatic cholestasis, estrogen-induced cholestasis, drug-induced cholestasis, cholestasis of pregnancy, parenteral nutrition-associated cholestasis, progressive familial cholestasis (PFIC), Alagille syndrome, primary biliary cirrhosis (PBC), primary sclerosing cholangitis, ductopenic liver transplant rejection, liver transplant associated graft versus host disease, cystic fibrosis liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver disease, 20 and parenteral nutrition-associated liver disease; or a gastrointestinal disease selected from bile acid malabsorption, bile reflux gastritis, and inflammatory bowel disease.

25

16. The compound for use according to claim 15, wherein said condition mediated by FXR is non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 55829-WO-PCT	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2014/063948	International filing date (<i>day/month/year</i>) 04 November 2014 (04.11.2014)	Priority date (<i>day/month/year</i>) 05 November 2013 (05.11.2013)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NOVARTIS AG		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 4 sheets, including this cover sheet.																								
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	This report contains indications relating to the following items: <table style="width: 100%;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td style="width: 70%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	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
☒	Box No. I	Basis of the report																							
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☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																							
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☐	Box No. VI	Certain documents cited																							
☐	Box No. VII	Certain defects in the international application																							
☐	Box No. VIII	Certain observations on the international application																							
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 10 May 2016 (10.05.2016) Authorized officer Athina Nickitas-Etienne e-mail: pt04.pct@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2014/063948

International filing date (day/month/year)
04.11.2014

Priority date (day/month/year)
05.11.2013

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4162 C07D471/04 C07D491/052

Applicant
IRM LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ 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 Rule 43bis.1(a)(i) with regard to novelty, inventive step and 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

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Telephone No. +49 89 2399-0



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ 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 (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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	<u>1-25</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-25</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-25</u>
	No: Claims	
2. Citations and explanations

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 2007/140183 A1 (LILLY CO ELI [US]; BELL MICHAEL GREGORY [US]; DOTI ROBERT ANTHONY [US]) 6 December 2007 (2007-12-06)

D2 WO 2009/012125 A1 (LILLY CO ELI [US]; GENIN MICHAEL JAMES [US]; AGEJAS-CHICHARRO FRANCISCO) 22 January 2009 (2009-01-22)

2 Novelty

D1 and D2 disclose pyrazoles and isoxazoles as farnesoid X receptor (FXR) modulators. The current application differs from D1 and D2 due to the tricyclic core ring structure. Thus the subject matter of claims 1-25 meets the requirements of novelty pursuant to Article 33(2) PCT.

3 Inventive step

The current application discloses compounds as FXR modulators. D1 is the closest prior art for the assessment of inventive step and discloses pyrazoles having the same activity. The technical problem to be solved lies in the provision of further compounds as FXR modulators. The problem appears to have been solved by the compounds tested on pages 112-113 of the description. Given the structural differences between the current application and D1, the skilled person would not have predicted the qualitative retention of the desired activity as FXR modulators for the compounds of the current application. The intermediates of formula V according to claim 16 share the significant structural element of the final compounds and are therefore also inventive. Therefore the subject-matter of claims 1-25 appears to meet the requirements of Article 33(3) PCT.

4 As to claim 19, it should be noted that the patentability can be 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 use in a first or further medical treatment.