

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/US2015/025029	International filing date (day/month/year) 09.04.2015	Priority date (day/month/year) 11.04.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07J63/00 A61K31/58 A61K31/56 A61P31/18 C07F5/02 C07C309/65		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Telephone No. +31 70 340-0 
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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:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
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 forming part of 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>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

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

The closest state of the art consists of the following document:

D1 WO-A-2013/123019

1) Claim 17 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT and Rule 67.1(iv) PCT. 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. Patentability, in particular novelty and inventive step, of claim 17 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

V.N - Novelty (Article 33(2) PCT)

2) Claim 1 relates to a general formula of lupane derivatives which are substituted in position 17 by an amine group (which may or may not be separated from position 17 by a methylene or carbonyl group "W"). These compounds also possess a 3-substituent which is a non-aromatic cyclic group ("X") substituted by two further groups:

- Group "Y", which is chosen from a group of various, mostly hydrophilic, chemical moieties, in particular a carboxyl group.
- Group "A", a haloalkyl group.

3) Claim 19 specifies a number of individual compounds, some of which fall within the scope of claim 1 and some of which do not. However, whether or not these compounds fall within the scope of claim 1 depends on the substituents which exist on the amine group attached directly or indirectly to position 17 and not on the 3-substituent. All of the 3-substituents of all of the compounds of claim 19 are the same as those defined for the compounds of claim 1. Likewise, claim 22 defines a general formula which overlaps with that of claim 1, but which also covers compounds not covered by claim 1. Again the differences between the formulae of claims 1 and 22 lies in the substituents on the C17-amine group, the definitions of the substituent in position 3 is identical between claims 1 and 22.

4) The compounds of the closest state of the art are disclosed in D1, examples A10-A13. These compounds differ from those of claims 1, 19 and 22 of the present application, only in that the non-aromatic cyclic substituent in position 3 is not

substituted by a haloalkyl group, but rather by a hydroxyalkyl group. In particular, these compounds of D1 have, as the preferred compounds of claim 19, a carboxyl substituent attached to the same position as the substituted alkyl substituent.

5) Consequently, the compounds of claims 1 and 2-12, 21 dependent thereon and of claims 19 and 22 are all novel according to Article 33(2) PCT, since they all contain this feature (the haloalkyl group substituted on the non-aromatic cyclic substituent in position 3 of the lupane structure). Furthermore, the compositions of these compounds according to claims 13-15 and 20, the medicinal indications thereof according to claim 16 and the medicinal uses thereof according to claim 17 are also all novel according to Article 33(2) PCT.

6) The intermediate compounds of claim 18 correspond to the preferred 3-substituents of the final products of claim 19. These are all reactive derivatives of cyclohexene substituted in position 4 by a carboxyl group (protected) and a fluoromethyl (=haloalkyl) group and in position 1 by a reactive group, enabling its introduction onto the 3-position of the lupane structure. These intermediate compounds differ over the corresponding intermediates of examples A10-A13 of D1 in that they have a fluoromethyl substituent, whereas the corresponding intermediates of D1 have a group corresponding to the hydroxyalkyl group of the final product (in particular in example A13, this precursor of the hydroxymethyl group is a carboxyl group which is reduced at the end of the reaction sequence). Consequently, the intermediate compounds of claim 18 are also novel over D1 according to Article 33 (2) PCT and for the same reason as the compounds of claims 1, 19 and 22.

V.IS - Inventive Step (Article 33(3) PCT)

7) The compounds of the present application are directed to solving the problem of the provision of agents for the treatment of HIV (see page 1, lines 10-13 of the description). In this regard it is noted that the applicant has provided comparative data, whereby compounds A and B (see page 317 of the description) are compared in terms of their anti-HIV activity with the compounds 2, 2a and 2b of the present application. However, the compounds A and B of D1 with which the comparison is made are not those of the closest state of the art, since compound A has a fluorine substituent directly attached to the non-aromatic substituent in position 3 and compound B has an *unsubstituted* methyl group attached to this same non-aromatic substituent. The compound of the closest state of the art with respect to compound 2 of the present application, is example A12 of D1, which is the same in every respect as compound 2 of the present application and which, like compound 2 has a *substituted* methyl group, the only difference being in compound A12 of D1, this substituent is an OH group, whereas in compound 2 it is an F atom. Consequently,

the present comparative tests do not demonstrate that the replacement of the of OH group of the compounds of D1 with the F-atom of the compounds of claims 1, 19 and 22 results in any advantageous properties. Consequently, the problem to be solved is the provision of further anti-HIV agents. Furthermore, even if a surprising improvement had been demonstrated, this would only have been shown for the "F" atom and not for other halogens, since no test results are given for chloro-, bromo- or iodo-alkyl derivatives.

8) Furthermore, the EC₅₀ results given for the tests in the present application are for the WT (wild type), A364V and 92UG029 mutants of HIV, whereas D1 appears to have used a recombinant NL₃₋₄ virus with the *nef* gene replaced by a reporter gene (*Renilla* luciferase). Consequently, the test results in D1 and those in the present application do not appear to be directly comparable.

9) In this regard it is noted that the only difference between the compounds of D1 and those of claims 1, 19 and 22 is that an OH group of the compounds of D1 has been replaced with a halogen atom (the test results for these compounds of examples A10-A13 are given on pages 237-238 of D1). Since it is well known that both OH and halogen atoms are polar groups and further given that D1 shows that the non-aromatic cyclic substituent in position 3 of the lupane structure can tolerate a variety of substituents in addition to the carboxy group (see the test results of D1 on pages 233-243), in particular both OH and halogen atoms can be attached directly to the non-aromatic ring (see compounds 11 and A9), it is evident to the skilled person that replacing one well known polar substituent (OH) with another well known polar substituent (halogen) in compounds A10-A13 will result compounds retaining their activity in treating HIV and falling within the scope of claims 1, 19 and 22.

Consequently, the compounds of these claims are an evident solution to the above mentioned problem and, as such, lack inventive step according to Article 33(3) PCT as do the compositions of these compounds according to claims 13-15 and 20, the medicinal indications thereof according to claim 16 and the medicinal uses thereof according to claim 17.

10) Furthermore, none of the dependent compound claims 2-12 and 21 (depending on claim 1) appear to contain any technical features which might render these claims inventive in their own right and as such, these compounds of these claims likewise lack inventive step according to Article 33(3) PCT.

11) Still further, the intermediate compounds of claim 18 are used in an analogy process to produce the compounds of claims 1, 19 and 22 and so the inventive step of these intermediates depends on their delivering an inventive final product (since these intermediates are differentiated over the corresponding intermediates of

examples A10-A13 of D1 in the same way as the final products of claims 1, 19 and 22 are differentiated over the final products of examples A10-A13 of D1 - namely the fluoromethyl substituent). Since the final haloalkyl substituted products of claims 1, 19 and 22 lack inventive step for the reasons given above, the fluoromethyl (=haloalkyl) intermediates of claim 18 likewise lack inventive step over the corresponding intermediates of D1 according to Article 33(3) PCT.

Re Item VIII

Certain observations on the international application

12) In the second proviso given in claim 1, on page 321, it is stated that:

"....only one of R_4 or R_5 can be selected from the group of $-COR_6$, $-COCOR_6$, $-SO_2R_7$ and $-SO_2NR_2R_2$;"

However, R_5 cannot represent the group COR_6 (it can be COR_3). Furthermore, neither R_4 nor R_5 can represent the group $-COCOR_6$. Consequently, this proviso is excluding compounds from claim 1, which are not covered by this claim. Consequently, claim 1 is rendered unclear by this contradiction.

13) All of the specific compounds of claim 12 fall within the scope of claim 1. Consequently, there is no reason why this should be formulated as an independent claim (Rule 6.4 PCT). This also means that claim 14 (specifying compositions containing the compounds of claim 12) should depend on claim 13 (specifying compositions containing the compounds of claim 1) according to Rule 6.4 PCT. Furthermore, the compound present in the compositions of claim 15 is the final compound of claim 12 and as such, claim 15 should also depend on either claim 13 or 14.

14) In claim 22, the value $-COOR_2$ appears twice in the definition of the variable group Y, thus rendering this claim inconcise according to Article 6 PCT.

15) In claim 22, the variable groups R_{18} and R_{19} are defined in this claim and yet these groups do not seem to appear elsewhere in the formula defined in this claim. Consequently, claim 22 is both unclear and inconcise according to Article 6 PCT.

16) The present application contains three independent compound claims (1, 19 and 22). All of these claims specify compounds having the same characterising feature (the haloalkyl substituent on the non-aromatic ring attached to position 3 of the lupane skeleton). Consequently, the present application contains an unnecessary proliferation of different general formulae (the general formulae of claims 1 and 22) and of independent compound claims (claims 1, 19 and 22) and as such is inconcise according to Article 6 PCT.