

EP Attorney Letter Head

Via Facsimile and Registered Mail

Xx October 2017

European Patent Office (Munich)
80298 Munich
Germany

Our Reference

XXXXX

European Patent Application No: 15155832.7
Applicant: ADVINUS
THERAPEUTICS LIMITED

This is in response to the communication dated 30th June 2017 issued by the European Patent Office under Article 94 (3) of EPC.

CLAIM AMENDMENTS

An amended set of claims 1-6 is submitted herein.

Applicant wishes to restrict claim 1 and its dependent claims to those compounds wherein pyrrolo [2,3-b] pyridine group is linked to bi-substituted phenyl ring on one side, and pyridine ring on the other side.

Claim 1 is also amended to delete compounds that contain pyrrolo[2,3-d]pyrimidine group.

Claim 1 is further amended to delete the compounds “8-cyclopropyl-4-[3-[2-[5-[(2,4-dimethylpiperazin-1-yl)methyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-6-fluoro-2,3-dihydro-1,4-benzoxazepin-5-one”, and “8-cyclopropyl-4-[3-[2-[5-[1-(3,4-dimethylpiperazin-1-yl)ethyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-6-fluoro-2,3-dihydro-1,4-benzoxazepin-5-one”.

Claims 2 to 6 remain unchanged.

No subject matter is abandoned by the present amendment and the Applicant reserves the right to reintroduce any subject matter and/or file a divisional application.

As none of the above amendments comprise subject matter extending beyond the application as originally filed, they should be allowable within the meaning of Article 123(2) EPC.

AMENDMENTS (Article 123(2) EPC)

In the present communication, the Examiner has acknowledged that the claim set as filed with our previous response of January 10, 2017 meets the requirements of article 123(2) EPC.

NOVELTY

In the present communication, the Examiner states “D1 page 145 lines 1-3 discloses a compound which together with claims 1 and 11-16, is seen as novelty hindering for claims 1-6 under Article 54(2) EPC”.

D1, on page 145 lines 1-3, discloses “8-cyclopropyl-4-[3-[2-[5-[1-(3,4-dimethylpiperazin-1-yl)ethyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-6-fluoro-2,3-dihydro-1,4-benzoxazepin-5-one”. With this response, claim 1 has been amended so as to exclude said compound from the list of compounds recited therein. Claim 1, as amended, is therefore novel over document D1. Claims 2-6 are novel by way of their dependency on amended claim 1.

INVENTIVE STEP

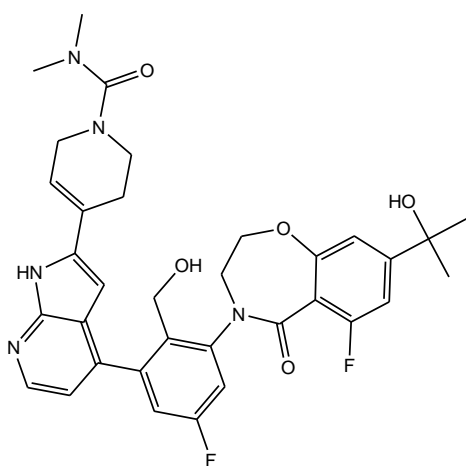
The Examiner states that the compounds of the present invention are not inventive according to Article 56 EPC. In particular, the Examiner states that since the compound raised in the novelty objection is also bi-substituted with a hydroxymethyl group and a fluorine at the central ring, there appears to be no difference between the compounds of D1 and the compounds claimed in the present application. The Examiner also states that D1 discloses a number of other compounds which are bi-substituted at the central ring, namely the compounds listed on page 145 lines 1 to 3, page 148 lines 1 to 24 and on page 170 lines 21 to 25 and page 183 lines 4 to 9 and 25 to 30 of D1. The Examiner therefore alleges that the claimed compounds are obvious alternatives to compounds disclosed in D1. Applicant respectfully disagrees.

In the present communication, the Examiner refers to compounds disclosed on page 145 lines 1 to 3, page 148 lines 1 to 24, page 170 lines 21 to 25 and page 183 lines 4 to 9 and 25 to 30 of D1. The Examiner indicates the compound disclosed on **page 145 lines 1 to 3** of D1, i.e., “8-cyclopropyl-4-[3-[2-[5-[1-(3,4-dimethylpiperazin-1-yl)ethyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-6-fluoro-2,3-dihydro-1,4-benzoxazepin-5-one” as novelty destroying for previous claim 1. As indicated above, Applicant has now amended claim 1 so as to delete said compound from the list of compounds recited therein. The

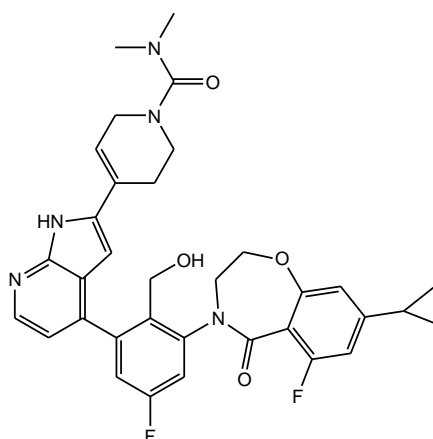
compound disclosed on **page 183 lines 28 to 30** of D1 is identical to the compound disclosed on **page 145 lines 1 to 3** of D1. Applicant notes that the compound disclosed on **page 183 lines 25 to 27** of D1 also anticipates the compounds of the present application. Therefore, this compound has also been deleted from claim 1 of the amended set of claims filed now.

The structural formulas of the compounds disclosed on page 148 lines 1 to 24 and on page 183 lines 4 to 9 of D1 are reproduced below:

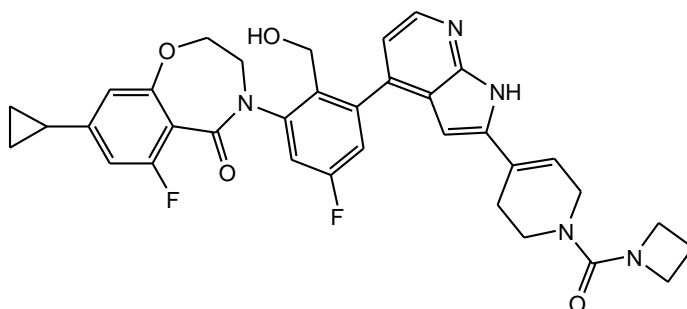
Page 148 lines 1 to 24 of D1:



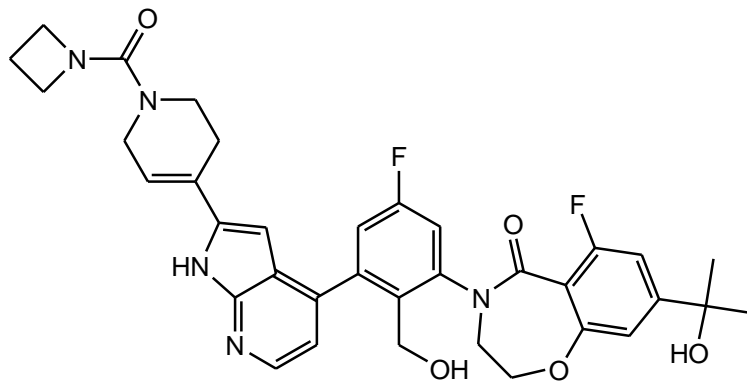
4-[4-[5-fluoro-3-[6-fluoro-8-(1-hydroxy-1-methyl-ethyl)-5-oxo-2,3-dihydro-1,4-benzoxazepin-4-yl]-2-(hydroxymethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-N,N-dimethyl-3,6-dihydro-2H-pyridine-1-carboxamide



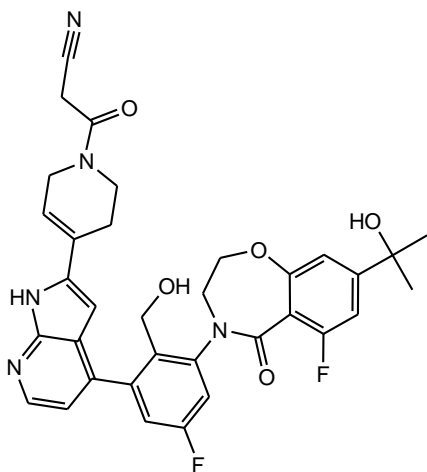
4-[4-[3-(8-cyclopropyl-6-fluoro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-N,N-dimethyl-3,6-dihydro-2H-pyridine-1-carboxamide



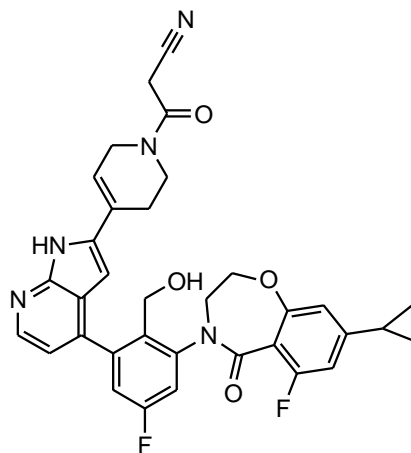
4-[3-[2-[1-(azetidine-1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-8-cyclopropyl-6-fluoro-2,3-dihydro-1,4-benzoxazepin-5-one



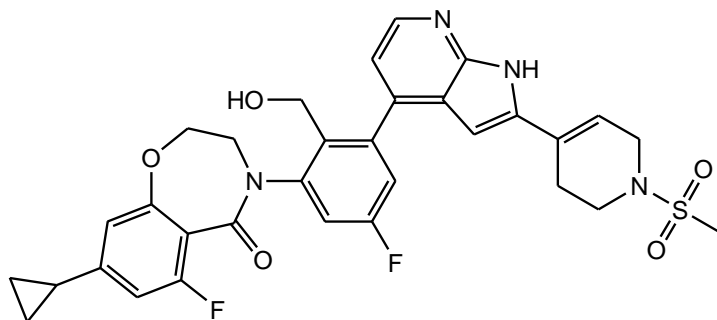
4-[3-[2-[1-(azetidine-1-carbonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-5-fluoro-2-(hydroxymethyl)phenyl]-6-fluoro-8-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-1,4-benzoxazepin-5-one



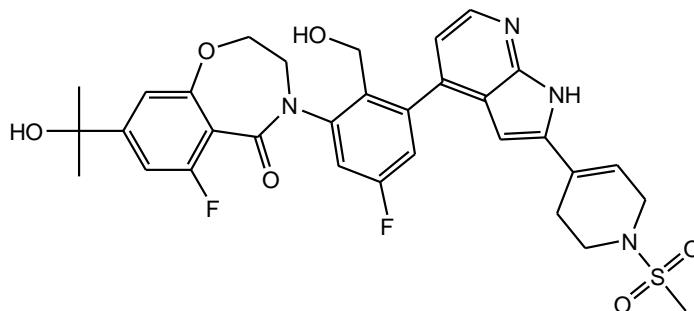
3-[4-[4-[5-fluoro-3-[6-fluoro-8-(1-hydroxy-1-methyl-ethyl)-5-oxo-2,3-dihydro-1,4-benzoxazepin-4-yl]-2-(hydroxymethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-3,6-dihydro-2H-pyridin-1-yl]-3-oxo-propanenitrile



3-[4-[4-[3-(8-cyclopropyl-6-fluoro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-1H-pyrrolo[2,3-b]pyridin-2-yl]-3,6-dihydro-2H-pyridin-1-yl]-3-oxo-propanenitrile

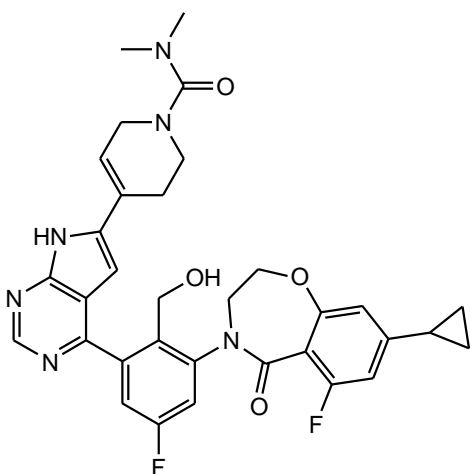


8-cyclopropyl-6-fluoro-4-[5-fluoro-2-(hydroxymethyl)-3-[2-(1-methylsulfonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one

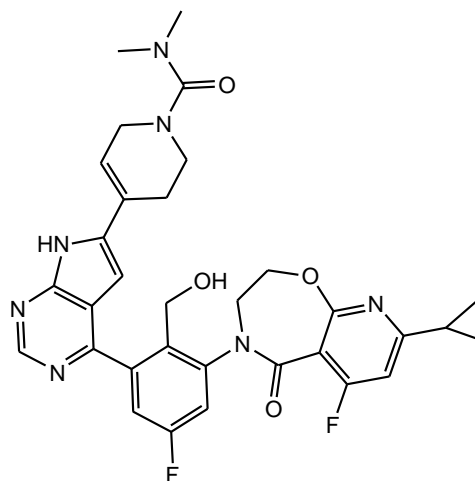


6-fluoro-4-[5-fluoro-2-(hydroxymethyl)-3-[2-(1-methylsulfonyl)-3,6-dihydro-2H-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-8-(1-hydroxy-1-methyl-ethyl)-2,3-dihydro-1,4-benzoxazepin-5-one

Page 183 lines 4 to 9 of D1:



4-[4-[3-(8-cyclopropyl-6-fluoro-5-oxo-2,3-dihydro-1,4-benzoxazepin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N,N-dimethyl-3,6-dihydro-2H-pyridine-1-carboxamide



4-[4-[3-(8-cyclopropyl-6-fluoro-5-oxo-2,3-dihydro-2,3-dihydropyrido[3,2-f][1,4]oxazepin-4-yl)-5-fluoro-2-(hydroxymethyl)phenyl]-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-N,N-dimethyl-3,6-dihydro-2H-pyridine-1-carboxamide

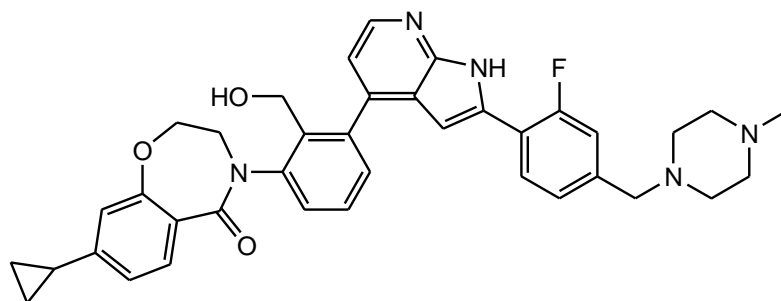
As shown by their structures, the compounds disclosed on page 148 lines 1 to 24 and page 183 lines 4 to 9 of D1 are substituted on the pyrrole portion of the 'pyrrolo-pyridine' or 'pyrrolo-pyrimidine' ring with a 3,6-dihydro-2H-pyridine group. In contrast, the compounds of the present invention contain a pyridine ring at the corresponding position. There is no disclosure or suggestion in D1 that would motivate one of ordinary skill in the art to substitute the 3,6-dihydro-2H-pyridine moiety of the compounds disclosed therein with a pyridine moiety. Further, the compounds disclosed on page 148 lines 1 to 24 and on page 183 lines 4 to 9 of D1 require

substitution at the ring nitrogen of the 3,6-dihydro-2H-pyridine group, while the compounds of the present invention require substitution on the ring carbon of the pyridine ring.

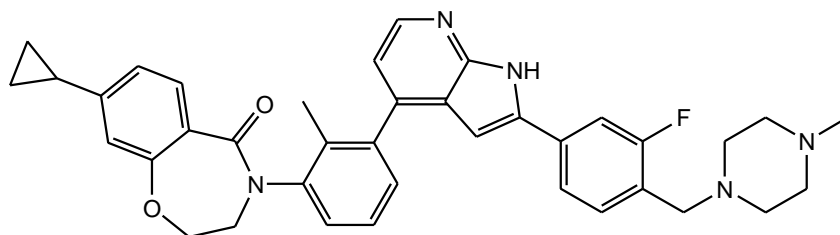
Without any disclosure or suggestion in D1 to make the necessary modifications to the compounds disclosed therein, there is no motivation for one of ordinary skill in the art to do so in order to arrive at the compounds of the present invention having BTK inhibitory activity. Accordingly, Applicant respectfully submits that D1 does not render obvious the compounds of the present invention.

The structural formulas of the compounds disclosed on page 170 lines 21 to 25 of D1 are reproduced below:

Page 170 lines 21 to 25 of D1:



8-cyclopropyl-4-[3-[2-[2-fluoro-4-[(4-methylpiperazin-1-yl)methyl]phenyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-2-(hydroxymethyl)phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one



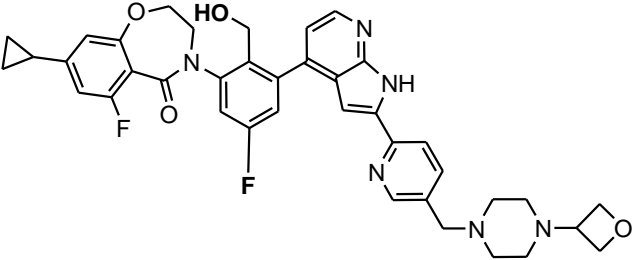
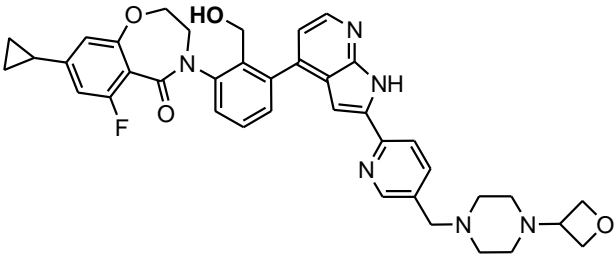
8-cyclopropyl-4-[3-[2-[3-fluoro-4-[(4-methylpiperazin-1-yl)methyl]phenyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]-2-methyl-phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one

Applicant respectfully submits that the compounds disclosed on page 170 lines 21 to 25 of D1 are structurally dissimilar to the instantly claimed compounds. For example, the compounds disclosed on page 170 lines 21 to 25 of D1 contain a pyrrolo [2,3-b] pyridine ring, which is linked via a ‘phenyl’ group to the piperazine moiety. In contrast, the pyrrolo [2,3-b] pyridine ring in the claimed compound is linked to the piperazine moiety via a ‘pyridine’ group. Without any disclosure or suggestion that such ‘pyridine’ functionality would be desirable, e.g. would lead to compounds having BTK inhibiting activity, there is no motivation for one of ordinary skill to make such modification in order to arrive at the instantly claimed compounds.

Applicant further respectfully directs the Examiner’s attention to the fact that the compounds of the present invention are bi-substituted with a hydroxymethyl group and a fluorine in the central phenyl ring, whereas the compounds disclosed on page 170 lines 21 to 25 of D1 have mono-substitution on the central phenyl ring. There is no disclosure or suggestion in D1 that introduction of a second substituent to the central phenyl ring would lead to further BTK inhibitors. Hence, the compounds as claimed in the present application are inventive over D1.

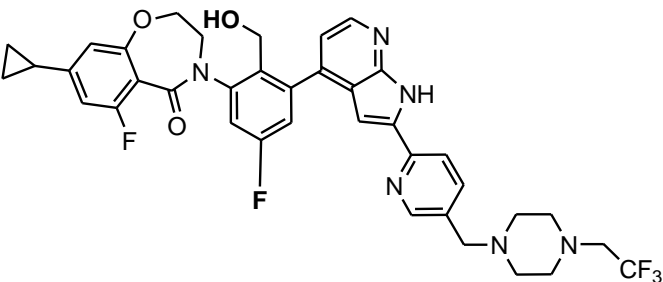
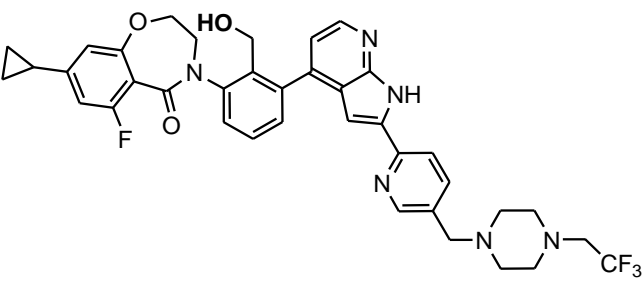
Further, the additional activity data presented in the below tables 1 and 2 provide further evidence that the instantly claimed compounds exhibit unexpected therapeutic advantage over the compounds of D1.

Table-1

Parameter	(Ex. 1 of the present application)	(Compound of D1)
	 <p>“8-cyclopropyl-6-fluoro-4-[5-fluoro-2-(hydroxymethyl)-3-[2-[5-[[4-(oxetan-3-yl)piperazin-1-yl]methyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one”</p>	 <p>“8-cyclopropyl-6-fluoro-4-[2-(hydroxymethyl)-3-[2-[5-[[4-(oxetan-3-yl)piperazin-1-yl]methyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one”</p>

	“ Bi-substitution - hydroxymethyl and fluorine substitution at the central phenyl ring”	“ Mono-substitution - hydroxymethyl substitution at the central phenyl ring”
hBTK1 IC₅₀ (nM)	0.9 ± 0.08 nM	1.4 ± 0.1 nM
Human whole blood assay IC₅₀	16.5 ± 5.5 nM	64.8 nM
Mino cell GIC₅₀	1.94 ± 0.3 μM (due to this potency the compound was selected for mouse xenograft model)	7.15 μM
ED₅₀	< 6 mg/kg in mouse xenograft model	Inadequate target engagement

Table-2

	(Ex. 2 of the present application)	(Compound of D1)
Parameter	 <p>“8-cyclopropyl-6-fluoro-4-[5-fluoro-2-(hydroxymethyl)-3-[2-[5-[[4-(2,2,2-trifluoroethyl)piperazin-1-yl]methyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one”</p> <p>“Bi-substitution - hydroxymethyl and fluorine substitution at the central phenyl ring”</p>	 <p>“8-cyclopropyl-6-fluoro-4-[2-(hydroxymethyl)-3-[2-[5-[[4-(2,2,2-trifluoroethyl)piperazin-1-yl]methyl]-2-pyridyl]-1H-pyrrolo[2,3-b]pyridin-4-yl]phenyl]-2,3-dihydro-1,4-benzoxazepin-5-one”</p> <p>“Mono-substitution - hydroxymethyl substitution at the central phenyl ring”</p>
hBTK1 IC₅₀ (nM)	2.6 ± 0.3 nM	1.6 nM
Human whole blood assay IC₅₀	89.6 ± 37 nM	361 ± 156 nM

Half life in rat	14.3 h (suitable for once daily dosing in humans)	6.6 h
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Based on the above, it is therefore respectfully submitted that the compounds of the present invention are not obvious and involve an inventive step over the disclosure of D1.

4. REQUESTS:

In light of the amendments and the arguments presented above, the Examining Division is respectfully requested to favorably reconsider the objections and allow this application to proceed to grant. The adaptation of the description is postponed until a final agreement on the wording of the claims has been reached.

If, however, the Examining Division does not agree with the above, it is requested that either a further Communication pursuant to Art. 116 EPC or an informal interview is requested. The undersigned is prepared to discuss minor amendments over the phone.

Yours Faithfully,

XXXXXX

Enclosures:

Marked-up copy of amended claims

Clean copy of amended claims.