Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Claims 1-18 are currently pending in the instant application.

Election/Restrictions

The Markush group set forth in the claims includes both independent and distinct inventions, and patentable distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentable distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentable distinct methods, also far too numerous to list individually**.** ***For these reasons provided below, restriction to one of the following Groups is required under 35 U.S.C. 121,*** wherein a Group is a set of patentable distinct inventions of a broad statutory category (e.g. compounds, methods of use, methods of making, etc.):

I Claims 1-11 drawn to a method of treating a Bruton's Tyrosine Kinase mediated disorder in a subject comprising administering a therapeutically effective amount of a compound of Formula (I) classified in A61K 31/4985.

II Claims 12-18 drawn to a combination of a compound of Formula (I) classified in C07D 487/04.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action,

different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group), i.e. they are patentable over each other. Chemical structures, which are similar, are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrefutable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

In accordance with the decisions in ***In re Harnisch***, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and ***Ex parte Hozumi,*** 3 USPQ 2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

The above groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Inventions I-II are related as products and their method of uses. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed could be used in materially different processes of using that product as demonstrated throughout the specification and in claims 1-11 for example, which are specifically directed to different method of using the products. Therefore, a separate search considerations are involved, which would impose a burden if unrestricted. Also, the fields of search are not coextensive. Additionally, besides performing a class/subclass search, the Examiner performs a commercial data base search and an automated patent system (text) search.

The products of Groups I-II differ materially in structure and in element. The invention Groups I-II outlined above relates to compounds and their methods of uses, which do not possess a substantial common core wherein a reference anticipating one would not necessarily render the other obvious and to search all the above groups in a single application would be an undue burden on the Examiner. In addition, because of the several classes and subclasses in each of the Group, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the examination of this application.

Where an election of any one of Group I-II is made, an election of a single compound is further required including an exact definition of each substitution on the base molecule, wherein a single member at each substituent group or moiety is selected. Upon the

election of a single disclosed compound (e.g. Example, page number and structural depiction), the scope of invention, inclusive of the elected compound, will be identified by the Examiner for examination along with the elected species. Moreover, whatever specific compound is ultimately elected, applicants are required to list all claims readable thereon. In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim, which fall into the same class and subclass as the elected compound, but may also include additional compounds, which fall in related subclasses. Examination will then proceed on the elected compound AND the entire scope of the invention encompassing the elected compound will be determined. A clear statement of the examined invention, defined by those class (es) and subclass (es) will be set forth in the first action on the merits. Note that the restriction requirement will not be made final until such time as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination. This will be set forth by reference to specific class(es) and subclass(es) examined. Should applicant traverse on the ground that the compound are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compound to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. (The provisions of 35 U.S.C. 121 applies with regard to double patenting covering divisional applications.)

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can **set forth** a group of compounds, which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Applicant is reminded that upon cancellation of claims to a nonelected invention, the inventions must be amended in compliance with 37 C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(i).

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification (subclasses), restriction for examination purpose as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purpose as indicated is proper.

Applicants preserve their right to file a divisional on the non-elected subject matter.

Advisory of Rejoinder

The following is a recitation of M.P.E.P. 821.04, Rejoinder:

> Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02(c) and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims, which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.
>
> Where the application as originally filed discloses the product and the process for making and/or using the product, and only claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product by way of amendment pursuant to 37 CFR 1.121. In view of the rejoinder procedure, and in order to expedite prosecution, applicants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution. Process claims, which depend from or otherwise include all the limitations of the patentable product, will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Amendments submitted after final rejections are governed by 37 CFR 1.116. Process claims, which do not depend from or otherwise include the limitations of the patentable product, will be withdrawn from consideration, via an election by original presentation (see MPEP § 821.03). Amendments submitted after allowance is governed by 37 CFR 1.312. Process claims which depend from or otherwise include all the limitations of an allowed product claim and which meet the requirements of 35 U.S.C. 101, 102, 103, and 112 may be entered.
>
> Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either: (A) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2); or (B) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2) even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26(a) states that "[T] he Commissioner may refund any fee paid by mistake or in excess of that required. A change of purpose after the payment of a fee...will not entitle a party to a refund of such fee..." In this case, the fees paid under 37 CFR 1.129(b) were not paid by mistake nor paid in excess, therefore, applicant would not be entitled to a refund. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101,102, 103, and 112. If the application containing the rejoined claims is not in condition for

> allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action. Form paragraphs 8.42 through 8.44 should be used to notify applicant of the rejoinder of process claims, which depend from or otherwise include all the limitations of an allowable product claim.
>
> In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.
>
> The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brower* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):
>
> "However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (Emphasis added)

Therefore, in accordance with M.P.EP 821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement is traversed (37 CFR 1.143).

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Golam Shameem, Ph.D., whose telephone number is (571) 272-

0706. The examiner can normally be reached on Monday-Thursday from 7:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane, can be reached at (571) 272-0699. The Unofficial fax phone number for this Group is (703) 308-7922. The Official fax phone numbers for this Group are (571) 273-8300. When filing a FAX in Technology Center 1600, please indicate in the Header (upper right) "Official" for papers that are to be entered into the file, and "Unofficial" for draft documents and other communications with the PTO that are not for entry into the file of the application. This will expedite processing of your papers.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [joseph.mckane@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via Internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified unless there is of record an express waiver of the confidentiality requirements under 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published by the Patent and Trademark Office Official Gazette on February 25, 1997 at 1195 OG 89.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR only. For more information about the pair system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (571) 272-1600.

/Golam M. M. Shameem/
Primary Examiner
Art Unit 1626
Technology Center 1600

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PUBLICATION NOTICE

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Publication No.US-2016-0151364-A1
Publication Date:06/02/2016

NOTICE OF PUBLICATION OF APPLICATION

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

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

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Bescheinigung	Certificate	Attestation
Die angehefteten Unterlagen stimmen mit der als ursprünglich eingereicht geltenden Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.	The attached documents are exact copies of the text in which the European patent application described on the following page is deemed to have been filed.	Les documents joints à la présente attestation sont conformes au texte, considéré comme initialement déposé, de la demande de brevet européen qui est spécifiée à la page suivante.

Patentanmeldung Nr.	**Patent application No.**	**Demande de brevet n°**
	11174578.2 / EP11174578	

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP11174578.

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le President de l'Office européen des brevets
p.o.

R.C. van Dijk

EPA/EPO/OEB Form 1014 12.08

Anmeldung Nr:
Application no.: 11174578.2
Demande no :

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Anmelder / Applicant(s) / Demandeur(s):

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Bezeichnung der Erfindung / Title of the invention / Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

BTK inhibitors

In Anspruch genommene Priorität(en) / Priority(Priorities) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

C07D487/00

Am Anmeldetag benannte Vertragstaaten / Contracting States designated at date of filing / Etats contractants désignées lors du dépôt:

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BTK inhibitors

Field of the invention

The present invention relates to 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

Background of the invention

B lymphocyte activation is key in the generation of adaptive immune responses. Derailed B lymphocyte activation is a hallmark of many autoimmune diseases and modulation of this immune response is therefore of therapeutic interest. Recently the success of B cell therapies in autoimmune diseases has been established. Treatment of rheumatoid arthritis (RA) patients with Rituximab (anti-CD20 therapy) is an accepted clinical therapy by now. More recent clinical trial studies show that treatment with Rituximab also ameliorates disease symptoms in relapsing remitting multiple sclerosis (RRMS) and systemic lupus erythematosus (SLE) patients. This success supports the potential for future therapies in autoimmune diseases targeting B cell immunity.

Bruton tyrosine kinase (Btk) is a Tec family non-receptor protein kinase, expressed in B cells and myeloid cells. The function of Btk in signaling pathways activated by the engagement of the B cell receptor (BCR) and FcεR1 on mast cells is well established. In addition, a function for Btk as a downstream target in Toll like receptor signaling was suggested. Functional mutations in Btk in human results in the primary immunodeficiency disease called XLA which is characterized by a defect in B cell development with a block between pro- and pre-B cell stage. This results in an almost complete absence of B lymphocytes in human causing a pronounced reduction of serum immunoglobulin of all classes. These finding support the key role for Btk in the regulation of the production of auto-antibodies in autoimmune diseases. In addition, regulation of Btk may affect BCR-induced production of pro-inflammatory cytokines and chemokines by B cells, indicating a broad potential for Btk in the treatment of autoimmune diseases.

With the regulatory role reported for Btk in FcεR-mediated mast cell activation, Btk inhibitors may also show potential in the treatment of allergic responses [Gilfillan et al, Immunological Reviews **288** (2009) pp149-169].

Furthermore, Btk is also reported to be implicated in RANKL-induced osteoclast differentiation [Shinohara et al, Cell **132** (2008) pp794-806] and therefore may also be of interest for the treatment of bone resorption disorders.

Other diseases with an important role for dysfunctional B cells are B cell malignancies. Indeed anti-CD20 therapy is used effectively in the clinic for the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia [Lim et al, Haematologica, **95** (2010) pp135-143]. The reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for Btk inhibitors in the treatment of B cell lymphomas as well. Inhibition of Btk seems to be relevant in particular for B cell lymphomas due to chronic active BCR signaling [Davis et al, Nature, **463** (2010) pp88-94].

Some classes of 6-5 membered fused pyridine ring compounds have been described as kinase inhibitors e.g. Imidazo[1,5-f][1,2,4]triazine compounds have been described in WO2005097800 and WO2007064993;. Imidazo[1,5-a]pyrazine compounds have been described in WO2005037836 and WO2001019828 as IGF-1R enzyme inhibitors.

Some of the Btk inhibitors reported are not selective over Src-family kinases. With dramatic adverse effects reported for knockouts of Src-family kinases, especially for double and triple knockouts, this is seen as prohibitive for the development of Btk inhibitors that are not selective over the Src-family kinases.

Both Lyn-deficient and Fyn-deficient mice exhibit autoimmunity mimicking the phenotype of human lupus nephritis. In addition, Fyn-deficient mice also show pronounced neurological defects. Lyn knockout mice also show an allergic-like phenotype, indicating Lyn as a broad negative regulator of the IgE-mediated allergic response by controlling mast cell responsiveness and allergy-associated traits [Odom et al, J. Exp. Med., **199** (2004) pp1491-1502]. Furthermore, aged Lyn knock-out mice develop severe splenomegaly (myeloid expansion) and disseminated monocyte/macrophage tumors [Harder et al, Immunity, **15** (2001) pp603-615]. These observations are in line with hyperresponsive B cells, mast cells and myeloid cells, and increased Ig levels observed in Lyn-deficient mice.

Female Src knockout mice are infertile due to reduced follicle development and ovulation [Roby et al, Endocrine, **26** (2005) pp169-176].

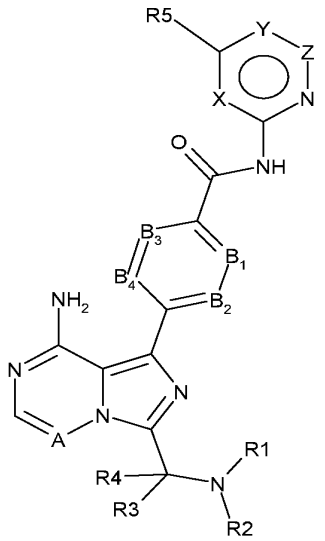
The double knockouts $Src^{-/-}Fyn^{-/-}$ and $Src^{-/-}Yes^{-/-}$ show a severe phenotype with effects on movement and breathing. The triple knockouts $Src^{-/-}Fyn^{-/-}Yes^{-/-}$ die at day 9.5 [Klinghoffer et al, EMBO J., **18** (1999) pp2459-2471]. For the double knockout $Src^{-/-}Hck^{-/-}$, two thirds of the mice die at birth, with surviving mice developing osteopetrosis, extramedullary hematopoiseis, anemia, leukopenia [Lowell et al, Blood, **87** (1996) pp1780-1792].

Hence, an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.

Detailed description of the invention

The object of the present invention is to provide 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

More specifically, the present invention provides 6-5 membered fused pyridine ring compounds according to formula I or pharmaceutically acceptable salts thereof.



Formula I

In this formula the substituents are defined as

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO_2 or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, halogen or (1-3C)alkoxy;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the carbon atom they are attached to a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, halogen or (1-3C)alkoxy;

R10 is H, halogen, or (1-3C)alkoxy;

R11 is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

R12 and R13 are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl.

With the proviso that:

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is C(R6) or N and X is C or N;
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

The terms as used herein refer to the following:

(1-2C)Alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl.

(1-3C)Alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl.

(1-4C)Alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred.

(1-5C)Alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, (1-4C)alkyl groups being preferred.

(1-6C)Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1-4C)alkyl being most preferred.

(1-2C)Alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined.

(1-3C)Alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)alkoxy groups are preferred.

(1-4C)Alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-3C)alkoxy groups are preferred, (1-2C)alkoxy groups being most preferred.

(2-4C)Alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl.

(2-6C)Alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl. (2-4C)alkenyl groups are preferred.

(2-4C)Alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl.

(2-6C)Alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (2-4C)alkynyl groups are preferred.

(3-6C)Cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

(3-7C)Cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

(2-6C)Heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom. Preferred heteroatoms are N or O. Preferred are piperidine, morpholine, pyrrolidine and piperazine. Most preferred (2-6C)heterocycloalkyl is pyrrolidine. The heterocycloalkyl group may be attached via a heteroatom if feasible.

(3-7C)Heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O. Preferred (3-7C) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl. More preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine. The heterocycloalkyl group may be attached via a heteroatom if feasible.

(3-7C)Cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom.

(6-10C)Aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl. The preferred (6-10C)aryl group is phenyl.

(1-5C)Heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S. The (1-5C)heteroaryl may optionally be substituted. Preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, more preferred (1-5C)heteroaryl is pyrimidyl.

(1-9C)Heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S. The (1-9C)heteroaryl may optionally be substituted. Preferred (1-9C)heteroaryl groups are quinoline, isoquinoline and indole.

[(1-4C)Alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined. Preferred [(1-4C)alkyl]amino group is methylamino.

Di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined. Preferred di[(1-4C)alkyl]amino group is dimethylamino.

Halogen means means fluorine, chlorine, bromine or iodine

(1-3C)Alkyl-C(O)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined.

(3-7C)Cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms. Preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl. Cyclohexenyl groups are most preferred.

(2-6C)Heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S. Preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that “all of the alkyl groups” of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula I indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term “substituted” means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. “Stable compound” or “stable structure” is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term “optionally substituted” means optional substitution with the specified groups, radicals or moieties.

Aspects of the invention

In one aspect the invention relates to a compound according to formula I wherein B1 is C(R7); B2 is C(R8); B3 is C(R9) and B4 is C(R10).

In another aspect the invention relates to a compound according to formula I wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10); R7, R9, and R10 each are H; and R8 is selected from a group consisting of hydrogen and methyl.
In one aspect the invention relates to a compound according to formula I wherein R8 is hydrogen or methyl, in particular R8 is hydrogen.

In another aspect the invention relates to a compound according to formula I wherein R7 is hydrogen, fluorine or (1-3C)alkoxy. In particular, R7 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to formula I wherein R7 is hydrogen.

In yet another aspect the invention relates to a compound according to formula I wherein R9 is hydrogen, fluorine or (1-3C)alkoxy. In particular, R9 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to formula I wherein R9 is hydrogen.

In another aspect the invention relates to a compound according to formula I wherein R10 is hydrogen fluorine or (1-3C)alkoxy. In particular, R10 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to formula I wherein R10 is hydrogen.

In still another aspect the invention relates to a compound according to formula I wherein R7 and R8 form, together with the carbon atom they are attached to, an indole or quinoline or naphtyl.

In another aspect the invention relates to a compound according to formula I wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10) and R7, R8, R9, and R10 each are H;

In yet another aspect the invention relates to a compound according to formula I wherein R4 is hydrogen or methyl. In particular, R4 is hydrogen.

In still another aspect the invention relates to a compound according to formula I wherein A is N.

In another aspect the invention relates to a compound according ot formula I wherein A is CH.

In another aspect the invention relates to a compound according to formula I wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl, and isoxazolyl. In particular, the invention relates to a compound according to formula I wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl and thiazolyl. The definition of R5 and R6 is independent from the selection of X, Y, and Z. The place of attachment of R5 and optionally of R6 to these heteroaryl rings follows from formula I.

The invention further relates to a compound according to formula I wherein R5 is selected from a group consisting of hydrogen, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy and (3-6C)cycloalkyl. All of the alkyl groups of R5 are optionally substituted with one or more halogen. In particular, the (1-4C)alkyl group in R5 is optionally substituted with one or more halogen.

In another aspect the invention relates to a compound according to formula I wherein R5 is selected from a group consisting of hydrogen, fluorine, chlorine, (1-3C)alkyl and (1-2C) alkoxy, all of the alkyl groups of R5 are optionally substituted with one or more halogen. In particular, the (1-3C)alkyl group in R5 is optionally substituted with one or more fluoro. Even more particularly, the invention relates to a compound according to formula I wherein R5 is hydrogen, fluorine, methyl, ethyl, propyl, methoxy or trifluoromethyl.

In yet another aspect the invention relates to a compound according to formula I wherein R5 is pyrrolidine or phenyl.

In another aspect, the invention relates to a compound according to formula I wherein R6 is hydrogen or (1-3C)alkyl, preferably R6 is hydrogen.

In yet another aspect the invention relates to a compound according to formula I wherein R5 and R6 together form a (3-7C)cycloalkenyl or a (2-6C)heterocycloalkenyl both optionally substituted with (1-3C)alkyl or one or more halogen. In particular, (3-7C)cycloalkenyl groups

are cyclohexenyl and cyclopentenyl. In particular, (2-6C)heterocycloalkenyl groups are azacyclohexenyl and oxocyclohexenyl. Even more in particularly, the invention relates to a compound according to formula I wherein the (3-7C)cycloalkenyl in R5 is cyclohexenyl..

In another aspect, the invention relates to a compound according to formula I wherein R2 is hydrogen or (1-3C)alkyl. In particular, R2 is hydrogen or methyl. R2 is hydrogen being most preferred.

In yet another aspect the invention relates to a compound according to formula I wherein R3 is (1-6C)alkyl. In particular, R3 is (1-3C)alkyl. R3 is methyl being most preferred.
In another aspect the invention relates to a compound according to formula I wherein R3 is (3-7C)cycloalkyl.

In another aspect the invention relates to a compound according to formula I wherein R2 is hydrogen or (1-3C)alkyl and R3 is (1-6C)alkyl. In particular, R2 is hydrogen or methyl and R3 is (1-3C)alkyl. Even more particularly, the invention relates to a compound according to formula I wherein R2 is hydrogen and R3 is methyl.

In yet another aspect the invention relates to a compound according to formula I wherein R2 or R3 are independently selected from a group consisting of cyclopropyl, cyclobutyl and cyclopentyl.

In another aspect the invention relates to a compound of formula I wherein,R2 and R3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more halogen, hydroxyl, (1-3C)alkyl. In particular, R2 and R3 form, together with the N and C atom they are attached to an azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl ring each optionally substituted with one or more halogen, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo, preferred halogen substituent being fluoro.
In yet another aspect the invention relates to a compound of formula I wherein, R2 and R3 form together with the N and C atom they are attached to an azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl ring each optionally substituted with fluoro, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo. In particular, R2 and R3 together with the N and C atom they are attached to form a pyrrolidinyl, piperidinyl, morpholinyl or homopiperidinyl ring.

In yet another aspect the invention relates to a compound according to formula I wherein, R1 is R11C(O) and R11 is (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl each optionally independently substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (1-3C)alkyl-S-C(O)-(1-3C)alkyl. In particular, the (1-

5C)heteroaryl group is pyrimidyl or triazinyl optionally substituted with one or more groups selected from halogen or cyano. In particular, the (3-7C)heterocycloalkyl is pyrrolidinyl. Even more particularly, the invention relates to a compound according to formula I wherein the (3-7C)cycloalkyl substituent of R11 is cyclopropyl. In particular, the (6-10C)aryl substituent of R11 is phenyl.

In yet another aspect the invention relates to a compound according to formula I wherein, R1 is C(O)R11 and R11 is (2-6C)alkenyl or (2-6C)alkynyl each optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, (di)[(1-4C)alkyl]amino, (1-3C)alkoxy or (3-7C)cycloalkoxy. In particular, the (3-7C)heterocycloalkyl substituent of R11 is pyrrolidinyl and the (3-7C)cycloalkyl substituent of R11 is cyclopropyl.

In another aspect the invention relates to a compound according to formula I wherein, R1 is C(O)R11 and R11 is (2-4C)alkenyl or (2-4C)alkynyl each optionally substituted with one or more groups selected from (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, (di)[(1-4C)alkyl]amino or (1-3C)alkoxy. In particular, the (3-7C)heterocycloalkyl substituent of R11 is pyrrolidinyl and the (3-7C)cycloalkyl substituent is cyclopropyl. Even more particularly, R11 is (2-4C)alkenyl or (2-4C)alkynyl each optionally substituted with one or more groups selected from methyl, ethyl, cyclopropyl, pyrrolidinyl, dimethylamino, methoxy or ethoxy.

In a further aspect the invention relates to compounds according to formula I wherein R1 is C(O)R11 wherein R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano. In particular, the (1-5C)heteroaryl substituent is pyrimidyl or triazinyl, pyrimidyl rings being preferred, optionally substituted with one or more groups selected from halogen or cyano. In particular, the halogen substituent is chlorine.

In another aspect, the invention relates to compounds according to formula I wherein R1 is $R13SO_2$, wherein R13 is (2-6C)alkenyl or (2-6C)alkynyl. In particular, R13 is (2-4C)alkenyl. Even more particularly, R13 is ethenyl.

In another aspect, the invention relates to compounds according to formula I wherein R1 is R12S(O), wherein R12 is (2-6C)alkenyl or (2-6C)alkynyl. In particular, R13 is (2-4C)alkenyl. Even more particularly, R12 is ethenyl.

In yet another aspect, the invention relates to compounds according to formula I wherein R1 is (1-3C)alkyl optionally substituted with R14 wherein R14 is (2-4C)alkenyl or (2-4C)alkynyl.

In yet another aspect the invention relates to a compound according to formula I selected from the group consisting of

(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,

(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,

(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,
4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-S-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate,
(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-methoxypyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl) imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,
4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide,
4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide,

(*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-N-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,
4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide, and
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide.

The invention also relates to those compounds wherein all specific definitions for R1 through R14 and all substituent groups in the various aspects of the inventions defined here above occur in any combination within the definition of the 6-5 membered fused pyridine ring

compounds i.e. 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds of formula I.

The 6-5 membered fused pyridine ring compounds like 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds of the invention inhibit the Btk kinase activity. All compounds of the invention have an EC50 of 10 μM or lower.

In another aspect the invention relates to compounds of formula I which have an EC50 of less than 100 nM. In yet another aspect the invention relates to compounds of formula I which have an EC50 of less than 10 nM.

The term EC50 means the concentration of the test compound that is required for 50% inhibition of its maximum effect in vitro.

Inhibition of kinase activity can be measured using the Immobilized Metal Assay for Phosphochemicals (IMAP) assay. IMAP is a homogeneous fluorescence polarization (FP) assay based on affinity capture of phosphorylated peptide substrates. IMAP uses fluorescein-labeled peptide substrates that, upon phosphorylation by a protein kinase, bind to so-called IMAP nanoparticles, which are derivatized with trivalent metal complexes. Binding causes a change in the rate of the molecular motion of the peptide, and results in an increase in the FP value observed for the fluorescein label attached to the substrate peptide (Gaudet et al. A homogeneous fluorescence polarization assay adaptable for a range of protein serine/threonine and tyrosine kinases. J. Biomol. Screen (2003) 8, 164-175).

The compounds of Formula (I) can form salts which are also within the scope of this invention. Reference to a compound of Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts. Salts of the compounds of Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of

pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g. substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and

diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (e.g, a drug precursor) that is transformed in vivo to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, “Pro-drugs as Novel Delivery Systems,” Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of the compounds listed.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The present invention also relates to a pharmaceutical composition comprising 6-5 membered fused pyridine ring compounds like imidazopyrazine and imidazotriazine compounds or pharmaceutically acceptable salts thereof having the general formula I in admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries

must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The invention further includes a compound of formula I in combination with one or more other drug(s).

Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, intramuscular, nasal, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used.

Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day, or,

in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of 6-5 membered fused pyridine ring compounds or a pharmaceutically acceptable salt thereof, having the general formula I for the manufacture of a medicament to be used for the treatment of Btk-mediated diseases or Btk-mediated conditions.

A further aspect of the invention resides in the use of 6-5 membered fused pyridine ring compounds or a pharmaceutically acceptable salt thereof having the general formula I for the manufacture of a medicament to be used for the treatment of chronic B cell disorders in which T cells play a prominent role.

In yet another aspect the invention resides in the use of 6-5 membered fused pyridine ring compounds like 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds having the general formula I for the manufacture of a medicament to be used for the treatment of Btk-mediated diseases or conditions. These include, but are not limited to, the treatment of B cell lymphomas resulting from chronic active B cell receptor signaling.

Thus, the compounds according to the invention can be used in therapies to treat or prevent diseases Bruton's Tyrosine Kinase (Btk) mediated disorders. Btk mediated disorders or Btk mediated condition as used herein, mean any disease state or other deleterious condition in which B cells, mast cells, myeloid cells or osteoclasts play a central role. These diseases

include but are not limited to, immune, autoimmune and inflammatory diseases, allergies, infectious diseases, bone resorption disorders and proliferative diseases.

Immune, autoimmune and inflammatory diseases that can be treated or prevented with the compounds of the present invention include rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis and spondylitis), glomerulonephritis (with or without nephrotic syndrome), autoimmune hematologic disorders (e.g. hemolytic anemia, aplasic anemia, idiopathic thrombocytopenia, and neutropenia), autoimmune gastritis, and autoimmune inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, schleroderma, diabetes (type I and type II), active hepatitis (acute and chronic), pancreatitis, primary billiary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosis, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis (e.g. Behcet's disease) chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease (e.g. chronic obstructive pulmonary disease) and other inflammatory or obstructive disease on airways.

Allergies that can be treated or prevented include, among others, allergies to foods, food additives, insect poisons, dust mites, pollen, animal materials and contact allergans, type I hypersensitivity allergic asthma, allergic rhinitis, allergic conjunctivitis.

Infectious diseases that can be treated or prevented include, among others, sepsis, septic shock, endotoxic shock, sepsis by Gram-negative bacteria, shigellosis, meningitis, cerebral malaria, pneumonia, tuberculosis, viral myocarditis, viral hepatitis (hepatitis A, hepatitis B and hepatitis C), HIV infection, retinitis caused by cytomegalovirus, influenza, herpes, treatment of infections associated with severe burns, myalgias caused by infections, cachexia secondary to infections, and veterinary viral infections such as lentivirus, caprine arthritic virus, visna-maedi virus, feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Bone resorption disorders that can be treated or prevented include, among others, osteoporosis, osteoarthritis, traumatic arthritis, gouty arthritis and bone disorders related with multiple myeloma.

Proliferative diseases that can be treated or prevented include, among others, non-Hodgkin lymphoma (in particular the subtypes diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)), B cell chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL) with mature B cell, ALL in particular.

In particular compounds of the invention can be used for the treatment of B cell lymphomas resulting from chronic active B cell receptor signaling.

Inhibition of kinase activity can be measured using the Immobilized Metal Assay for Phosphochemicals (IMAP) assay. IMAP is a homogeneous fluorescence polarization (FP) assay based on affinity capture of phosphorylated peptide substrates. IMAP uses fluorescein-labeled peptide substrates that, upon phosphorylation by a protein kinase, bind to so-called IMAP nanoparticles, which are derivatized with trivalent metal complexes. Binding causes a change in the rate of the molecular motion of the peptide, and results in an increase in the FP value observed for the fluorescein label attached to the substrate peptide.

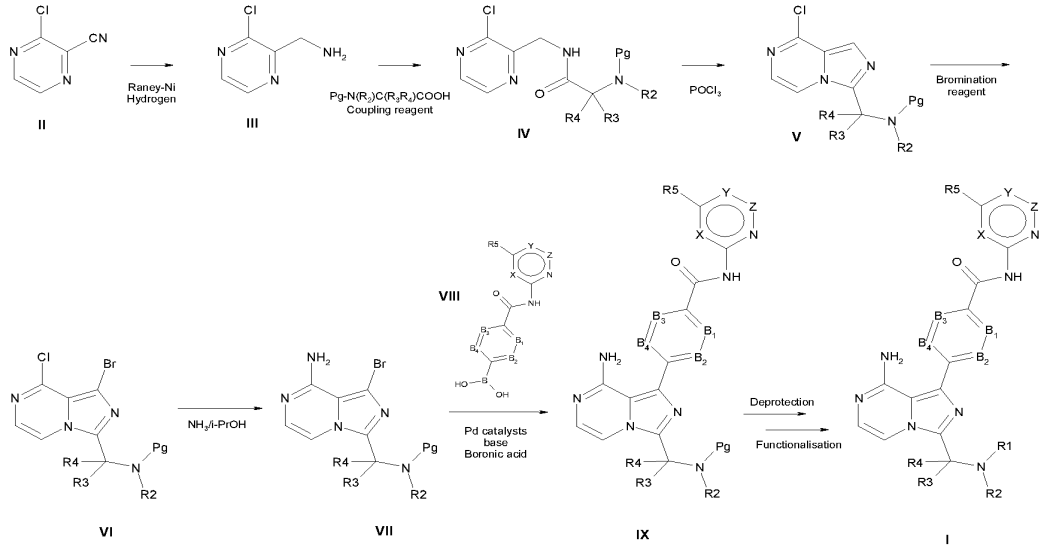
The Btk activity can also be determined in B cell lines such as Ramos cells or in primary cell assays, e.g PBMC or whole blood from human, monkey, rat or mouse or isolated splenocytes from monkey, rat or mouse. Inhibition of Btk activity can be investigated measuring anti-IgM-induced MIP1β production (Ramos, PBMC, splenocytes), H_2O_2-induced Btk and PLCγ2 phosphorylation (Ramos cells), or anti-IgM-induced B cell proliferation or CD86 expression on primary B cells (PBMC and splenocytes).
Regulation of Btk activity can also be determined on human, monkey, rat or mouse mast cells following activation FcεR induced degranulation, cytokine production and CD63 induced cell surface expression.
Furthermore, regulation of Btk activity can be determined on CD14+ monocytes differentiated following treatment with M-CSF to osteoclasts and activated with RANKL.

Activity of Btk inhibitors can be investigated in mouse splenocytes following administration *in vivo*. In a typical experiment mice can be euthanized 3h following compound administration. Spleens can be extracted from the treated mice for splenocyte isolation. Splenocytes can be plated in 96 well culture plates and stimulated with anti-IgM, without further addition of compounds. Anti-IgM-induced B cell stimulation and inhibition thereof by Btk inhibitors can be measured by B cell proliferation, MIP1β production or CD86 expression on CD19+ splenocyte B cells.
Efficacy of Btk inhibitors can also be investigated in the mouse collagen induced arthritis model using a therapeutic protocol with start of treatment following onset of disease, measuring disease score, X-ray analysis of bone destruction, cartilage breakdown and histology of joints
Efficacy of Btk inhibitors on the regulation of activated mast cells can be investigated in vivo using the passive cutaneous anaphylaxis model.
The effect of Btk inhibitors on bone resorption in vivo can be investigated using the rat OVX model. In this model ovariectomized animals develop symptoms of osteoporosis that may be regulated using a Btk inhibitor.

General Synthesis

The 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention can be prepared by methods well known in the art of organic chemistry. See, for example, J. March, '*Advanced Organic Chemistry*' 4th Edition, John Wiley and Sons. During synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This is achieved by means of conventional protecting groups, such as those described in T.W. Greene and P.G.M. Wutts '*Protective Groups in Organic Synthesis*' 3rd Edition, John Wiley and Sons, 1999. The protective groups are optionally removed at a convenient subsequent stage using methods well known in the art. The products of the reactions are optionally isolated and purified, if desired, using conventional techniques, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials are optionally characterized using conventional means, including physical constants and spectral data.

8-amino-imidazo[1,5-a]pyrazine compounds of formula I, wherein R_1-R_5 have the previously defined meanings, can be prepared by the general synthetic route shown in scheme I



Scheme I

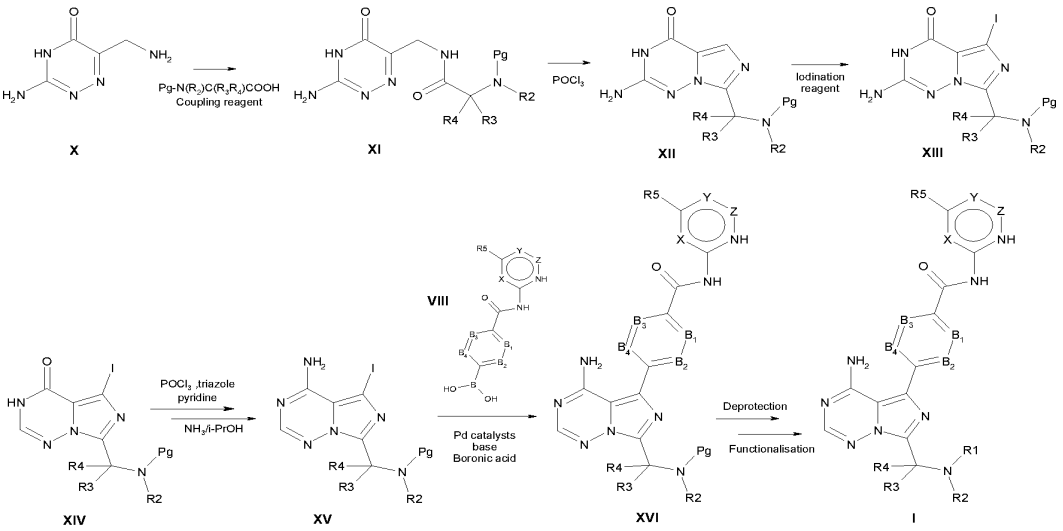
Reduction of 3-chloropyrazine-2-carbonitrile (**II**) can be accomplished by hydrogenation in the presence of a suitable catalysts system and solvent, for example Raney-Nickel to provide (3-chloropyrazin-2-yl)methanamine (**III**). This can then be reacted with an appropriately amine protected amino acid. The reaction of Cbz-N(R_2)CR_3R_4)COOH can be carried out in a solvent such as DMF, THF or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, 4-DMAP or triethylamine and in the presence of a coupling reagent such as PyBOP, TBTU, EDCI or HATU to form N-((3-chloropyrazin-2-yl)methyl)amide **IV**. Cyclisation chloropyrazine **IV** can be performed using condensation reagents like phosphorousoxychloride under heating conditions to provide the 8-chloroimidazo[1,5-a]pyrazine derivatives **V**. Subsequent

bromination can be accomplished using bromine or N-bromosuccinimide in a suitable solvent like DCM or DMF at appropriate temperature to obtain compounds of formula **VI**. 8-Aminoimidazo[1,5-a]pyrazine derivatives (**VII**) can be prepared from compounds **VI** using ammonia(gas) in isopropanol at elevated temperature in a pressure vessel (>4 atm). Compounds of formula **IX** can be prepared from compounds of formula **VII** using an appropriate boronic acid or pinacol ester (**VIII**), in the presence of a suitable palladium catalyst system and solvent, for example bis(diphenylphosphino)ferrocene palladium(II)chloride complex or *tetrakis*(triphenylphosphine)palladium(0) in the presence of potassium carbonate in dioxane/water provide compounds of formula **IX**. Finally, cleaving the protective group of compounds with the formula **IX** give the unprotected amine which after functionalisation, using methods well known in the art, with appropriate warheads with previously defined meanings, provided compounds of formula **I**. An example of such protective strategy is the use of the benzyloxycarbonyl protecting group to protect the amine from the amino acids used, and after deprotection with 33% HBr/HOAc or conc. HCl gave the resulting amines.

The amino acids $HN(R_2)CR_3R_4)COOH$ are either commercially available or they can be readily prepared using methods well known to the skilled organic chemist, to introduce protecting groups like benzyloxycarbonyl or *tert*-butyloxycarbonyl.

Palladium catalysts and conditions to form either the pinacol esters or to couple the boronic acids or pinacol esters with the 1-bromoimidazo[1,5-a]pyrazin-8-amine are well known to the skilled organic chemist – see, for example, Ei-ichi Negishi (Editor), Armin de Meijere (Associate Editor), Handbook of Organopalladium Chemistry for Organic Synthesis, John Wiley and Sons, 2002.

4-Amino-imidazo[1,5-f][1,2,4]triazine compounds of formula I, wherein R_1-R_5 have the previously defined meanings, can be prepared by the general synthetic route shown in scheme II



Scheme II

Starting material 3-amino-6-(aminomethyl)-1,2,4-triazin-5(4H)-one **X** can be prepared via a condensation reaction of ethyl bromopyruvate, dibenzylamine, and aminoguanidine carbonate, followed by debenzylation via hydrogenation over Pd-C catalyst [Mitchel, W.L.et al, *J. Heterocycl. Chem.* **21** (1984) pp697].This can then be reacted with an appropriately amine protected amino acid. The reaction of Cbz-N(R_2)CR_3R_4)COOH can be carried out in a solvent such as DMF, THF or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, 4-DMAP or triethylamine and in the presence of a coupling reagent such as PyBOP, TBTU, EDCI or HATU to form N-((3-amino-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl)amide **XI**. Cyclisation of the amino-triazinone **XI** can be performed using condensation reagents like phosphorousoxychloride under heating conditions to provide the 2-aminoimidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XII**. Subsequent iodination can be accomplished using iodine or N-iodosuccinimide in a suitable solvent like DCM or DMF at appropriate temperature to obtain compounds of formula **XIII**. Removal of the 2-amino group in the 2-aminoimidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XIII** can be perfomed using t-butyl nitrite in solvents like DMF/THF at room temperature to form imidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XIV**. 4-Amino-imidazo[1,5-f][1,2,4]triazine derivatives (**XV**) can be prepared from compounds **XIV** using phosphorousoxychloride, 1,2,4-triazole in pyridine and subsequent ammonolysis with ammonia(gas) in isopropanol at room temperature. Compounds of formula **XVI** can be prepared from compounds of formula **XV** using an appropriate boronic acid or pinacol ester (**VIII**), in the presence of a suitable palladium catalyst system and solvent, for example bis(diphenylphosphino)ferrocene palladium(II)chloride complex or *tetrakis*(triphenylphosphine)palladium(0) in the presence of potassium carbonate in dioxane/water provide compounds of formula **XVI**. Finally, cleaving the protective group of compounds with the formula **XVI** give the unprotected amine which after functionalisation, using methods well known in the art, with appropriate warheads with previously defined meanings, provided compounds of formula **I**. An example of such protective strategy is the use of the benzyloxycarbonyl protecting group to protect the amine from the amino acids used, and after deprotection with 33% HBr/HOAc or conc. HCl gave the resulting amines.

The amino acids HN(R_2)CR_3R_4)COOH are either commercially available or they can be readily prepared using methods well known to the skilled organic chemist, to introduce protecting groups like benzyloxycarbonyl or *tert*-butyloxycarbonyl.

Palladium catalysts and conditions to form either the pinacol esters or to couple the boronic acids or pinacol esters with the 5-iodoimidazo[1,5-f][1,2,4]triazin-4-amine are well known to the skilled organic chemist – see, for example, Ei-ichi Negishi (Editor), Armin de Meijere (Associate Editor), Handbook of Organopalladium Chemistry for Organic Synthesis, John Wiley and Sons, 2002.

The present invention also includes within its scope all stereoisomeric forms of the 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives according to the

present invention resulting, for example, because of configurational or geometrical isomerism. Such stereoisomeric forms are enantiomers, diastereoisomers, *cis* and *trans* isomers *etc.* For example where azepane-2-carboxylic acid is used as amino acid, there exists a mixture of two enantiomers. In the case of the individual stereoisomers of compounds of formula I or salts or solvates thereof, the present invention includes the aforementioned stereoisomers substantially free, *i.e.*, associated with less than 5%, preferably less than 2% and in particular less than 1% of the other stereoisomer. Mixtures of stereoisomers in any proportion, for example a racemic mixture comprising substantially equal amounts of two enantiomers are also included within the scope of the present invention.

For chiral compounds, methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, *e.g.* synthesis with chiral induction, synthesis starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers using chromatography on chiral media. Such methods are described in *Chirality In Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Likewise methods for synthesis of geometrical isomers are also well known in the art.

The8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of formula I with an organic or inorganic acid such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

The8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention also exist as amorphous forms. Multiple crystalline forms are also possible. All the physical forms are included within the scope of the present invention.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into

compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula I (e.g. those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herinbelow, by substituting an appropriate isotopically labeled reagent for a non-isotoplically labeled reagent.

The invention is illustrated by the following examples.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

Mass Spectrometry: Electron Spray spectra were recorded on the Applied Biosystems API-165 single quad mass spectrometer in alternating positive and negative ion mode using Flow Injection. The mass range was 120-2000 Da and scanned with a step rate of 0.2 Da. and the capillary voltage was set to 5000 V. N2-gas was used for nebulisation.

LC-MS spectrometer (Waters) Detector: PDA (200-320 nm), Mass detector: ZQ

Eluens : A: acetonitrile with 0.05% trifluoroacetic acid , B: acetronitrile / water = 1/9 (v/v) with 0.05% trifluoroacetic acid

Methode LCMS (A)

Column 1: Chromolith Performance, RP-18e, 4.6x100 mm,

Gradient method: Flow: 4 mL/min

Time (min)	A (%)	B (%)
0.00	100	0
3.60	0	100
4.00	0	100
4.05	100	0
6.00	100	0

Methode LCMS (B)

Column 2: XBridge C18, 3.5µm, 4.6x20mm

Gradiënt methoden: Flow: 4 ml/min

Time (min.)	A (%)	B (%)
0.0	100	0
1.60	0	100
3.10	0	100
3.20	100	0
5.00	100	0

UPLC : Water acquity UPLC system; Column : BEH C18 1.7 µm, 2.1 x 100 mm, Detector: PDA (200-320 nm), Mass detector: SQD

Eluens : A: acetonitrile with 0.035% trifluoroacetic acid , B: acetronitrile / water = 1/9 (v/v) with 0.035% trifluoroacetic acid

Methode	**UPLC (A)**		**UPLC (B)**		**UPLC (C)**	
	Method 60_100		*Method 40_80*		*Method 0_60*	
	Flow: 0.75 mL/min		Flow: 0.65 mL/min		Flow: 0.60 mL/min	
Time (min)	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
0.0	40	60	60	40	100	0
3.00	0	100	20	80	40	60
3.20	0	100	0	100	0	100
3.69	0	100	0	100	0	100
3.70	40	60	60	40	100	0

Preparative HPLC was conducted on a column (50 x 10 mm ID, 5µm, Xterra Prep MS C18) at a flow rate of 5 ml/min, injection volume 500 µl, at room temperature and UV Detection at 210 nm.

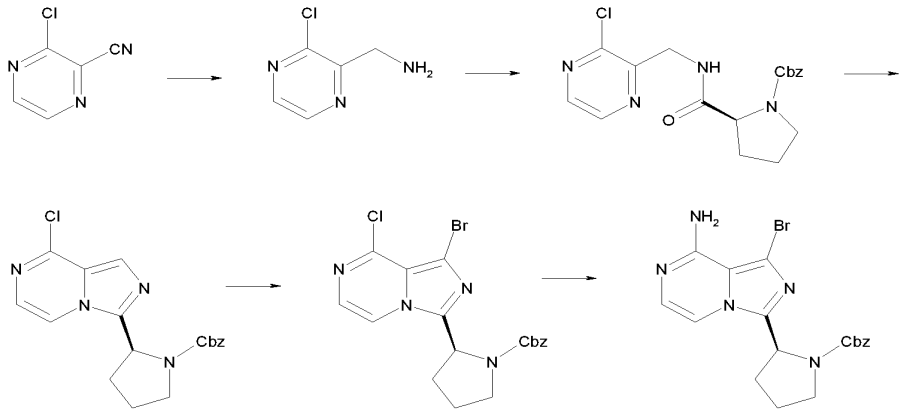
The following abbreviations are used throughout the application with respect to chemical terminology:

HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate
Cbz	Benzyloxycarbonyl
DMF	N,N-Dimethylformamide
DCM	Dichloromethane
EtOAc	Ethyl acetate
DIPEA	N,N-Diisopropylethylamine
THF	Tetrahydrofuran
EtOH	Ethanol
EDCI.HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide. hydrochloride
4-DMAP	4-Dimethylamino pyridine
PyBOP	O-Benzotriazole-1-yl-oxy-trispyrrolidinophosphonium

	hexafluorophosphate
TBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
HBr	Hydrogen bromide
HCl	Hydrogen chloride
HOAc	Acetic acid
Z	Benzyloxycarbonyl
Pro	Proline
$POCl_3$	Phosphorous oxychloride
HPLC	High Pressure Liquid Chromatography
UPLC	
LiHMDS	Lithium hexamethyldisilazide
MeOH	Methanol
Gly	Glycine
Ala	Alanine
n-BuLi	n-Butyllithium
CO_2	Carbondioxide

The names of the final products in the examples are generated using Chemdraw Ultra (version 9.0.7).

Intermediate 1



(*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(a) (3-Chloropyrazin-2-yl)methanamine.hydrochloride

To a solution of 3-chloropyrazine-2-carbonitrile (160 g, 1.147 mol) in acetic acid (1.5 L) was added Raney Nickel (50% slurry in water, 70 g, 409 mmol). The resulting mixture was stirred under 4 bar hydrogen at room temperature overnight. Raney Nickel was removed by filtration over decalite and the filtrate was concentrated under reduced pressure and co-evaporated with toluene. The remaining brown solid was dissolved in ethyl acetate at 50°C and cooled on an ice-bath. 2M hydrogen chloride solution in diethyl ether (1.14 L) was added in 30 min. The

mixture was allowed to stir at room temperature over weekend. The crystals were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C. The product brown solid obtained was dissolved in methanol at 60°C. The mixture was filtered and partially concentrated, cooled to room temperature and diethyl ether (1000 ml) was added. The mixture was allowed to stir at room temperature overnight. The solids formed were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C to give 153.5 g of (3-chloropyrazin-2-yl)methanamine.hydrochloride as a brown solid (74.4 %, content 77 %).

(b) (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate

To a solution of (3-chloropyrazin-2-yl)methanamine.HCl (9.57 g, 21.26 mmol, 40% wt) and Z-Pro-OH (5.3 g, 21.26 mmol) in dichloromethane (250 mL) was added triethylamine (11.85 mL, 85 mmol) and the reaction mixture was cooled to 0°C. After 15 min stirring at 0°C, HATU (8.49 g, 22.33 mmol) was added. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. The mixture was washed with 0.1 M HCl-solution, 5% $NaHCO_3$, water and brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 5 g of (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (62.7%).

(c) (*S*)-Benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(*S*)-Benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (20.94 mmol, 7.85 g) was dissolved in acetonitrile (75 ml), 1,3-dimethyl-2-imidazolidinone (62.8 mmol, 6.9 ml, 7.17 g) was added and the reaction mixture was cooled to 0ºC before $POCl_3$ (84 mmol, 7.81 ml, 12.84 g) was added drop wise while the temperature remained around 5ºC. The reaction mixture was refluxed at 60-65°C overnight. The reaction mixture was poured carefully in ammonium hydroxide 25% in water (250 ml)/crushed ice (500 ml) to give a yellow suspension (pH ~8-9) which was stirred for 15 min until no ice was present in the suspension. Ethyl acetate was added, layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give 7.5 g crude product. The crude product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 6.6 g of (*S*)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (88%).

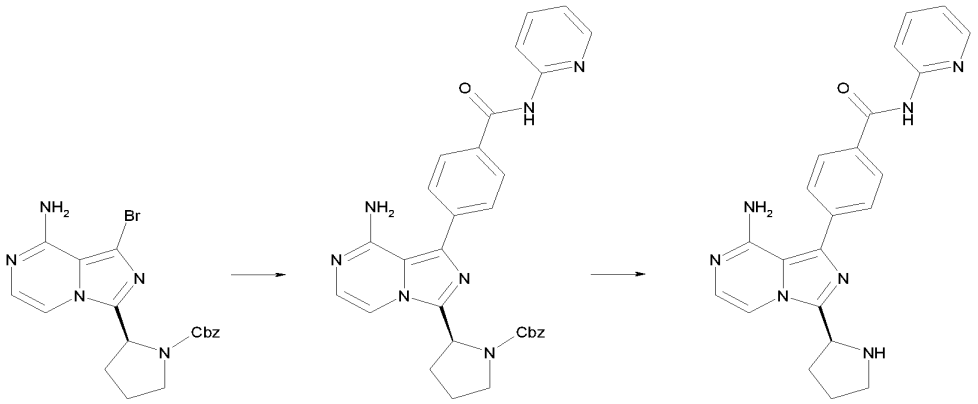
(d) (*S*)-Benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

N-Bromosuccinimide (24.69 mmol, 4.4 g) was added to a stirred solution of (*S*)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (24.94 mmol, 8.9 g) in DMF (145 mL). The reaction was stirred 3 h at rt. The mixture was poored (slowly) in a stirred mixture of water (145 mL), ethyl acetate (145 mL) and brine (145 mL). The mixture was then transferred into a separating funnel and extracted. The water layer was extracted with 2x145 mL ethyl acetate. The combined organic layers were washed with 3x300 mL water, 300 mL brine, dried over sodium sulfate, filtered and evaporated. The product was purified using silica gel chromatography (ethyl acetate/heptane = 3/1 v/v%) to give 8.95 g of (S)-benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (82.3%).

(e) (*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20.54 mmol, 8.95 g) was suspended in 2-propanol (113 ml) in a pressure vessel. 2-propanol (50 ml) was cooled to -78ºC in a pre-weighed flask (with stopper and stirring bar) and ammonia gas (646 mmol, 11 g) was lead through for 15 minutes. The resulting solution was added to the suspension in the pressure vessel. The vessel was closed and stirred at room temperature and a slight increase in pressure was observed. Then the suspension was heated to 110 °C which resulted in an increased pressure to 4.5 bar. The clear solution was stirred at 110 ºC, 4.5 bar overnight. After 18h the pressure remained 4 bar. The reaction mixture was concentrated in vacuum, the residue was suspended in ethyl acetate and subsequent washed with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 7.35 g of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (86%).

Intermediate 2



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

(a) (*S*)-Benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

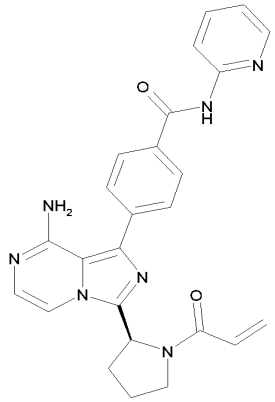
(S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.237 mmol, 98.5 mg) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (0.260 mmol, 63.0 mg) were suspended in a mixture of 2N aqueous potassium carbonate solution (2.37 mmol, 1.18 mL) and dioxane (2.96 mL). Nitrogen was bubbled through the mixture, followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene palladium (ii) chloride (0.059 mmol, 47.8 mg). The reaction mixture was heated for 20 minutes at 140°C in the microwave. Water was added to the reaction mixture, followed by an extraction with ethyl acetate (2x). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The product was purified using silicagel and dichloromethane/methanol = 9/1 v/v% as eluent to afford 97.1 mg of

(*S*)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (77%).

(b) (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.146 mmol, 78 mg) was added a 33% hydrobromic acid/acetic acid solution (11.26 mmol, 2 ml) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water and extracted with dichloromethane. The aqueous phase was neutralized using 2N sodium hydroxide solution, and then extracted with dichloromethane. the organic layer was dried over magnesium sulfate, filtered and evaporated to give 34 mg of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (58%).

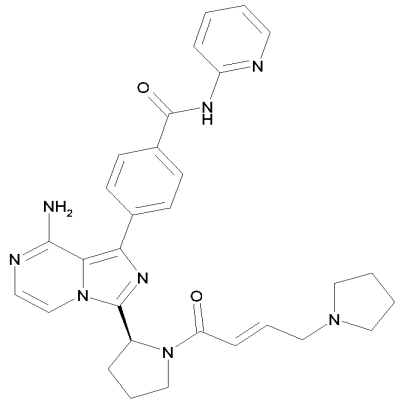
Example 1



(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a solution of (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (0.626 mmol, 250 mg) in dichloromethane (25 ml) at 0 °C was added triethylamine (0.626 mmol, 0.087 ml, 63.3 mg) and, drop wise, acryloyl chloride (0.657 mmol, 0.053 ml, 59.5 mg). The resulting mixture was stirred at 0 °C for 2 hours. The mixture was washed with water, dried over magnesium sulfate. After evaporation, the residue was purified by preparative HPLC. Fractions containing product were collected and lyophilized to afford 126 mg of (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (44.4% yield). Data: UPLC (C) R_t : 1.50 min; *m/z* 454.3 $(M+H)^+$.

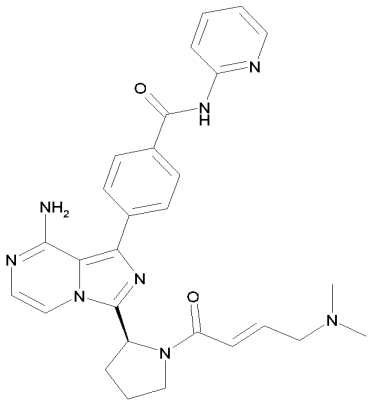
Example 2



(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a solution of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 2b, 19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) and (*E*)-4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride (9.45 mg, 0.049 mmol) in dichloromethane (2 mL) was added HATU (18.75 mg, 0.049 mmol). The mixture was stirred for 30 min at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by preparative HPLC. Fractions containing product were collected and reduced to dryness to afford 7.1 mg of (*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (26.8 % yield). Data: UPLC (C) R_t : 1.25 min; *m/z* 537.4 $(M+H)^+$.

Example 3



(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

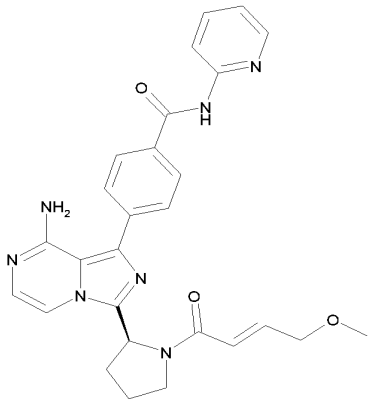
This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (11.8 mg, 46.6%). Data: UPLC (C) R_t : 1.29 min; *m/z* 511.0 $(M+H)^+$.

Intermediate 3

(*E*)-4-Methoxybut-2-enoic acid

Sodium methoxide (30%/Methanol, 30.3 mmol, 5.68 mL) was added via a glass syringe to a stirred solution of 4-bromocrotonic acid (6.06 mmol, 1 g) in methanol (60 mL) at room temperature. The light yellow solution was stirred for 30 min at room temperature and 2 h. at reflux. After cooling the reaction mixture, the solvent was removed under reduced pressure. The residue was partitioned between water (50 mL) and diethyl ether (50 mL). 2M aq. hydrochloride solution (3.5 mL) was added until pH was ~pH 1. The waterlayer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*, to give 650 mg of (*E*)-4-Methoxybut-2-enoic acid (92%).

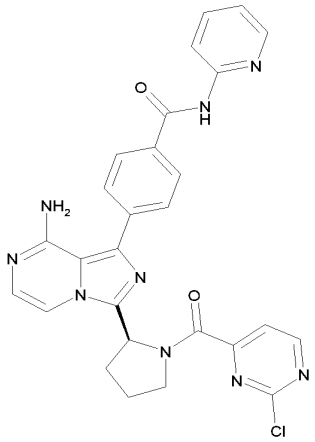
Example 4



(*S*,*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (11 mg, 29.9%). Data: UPLC (C) R_t : 1.58 min; *m/z* 498.3 $(M+H)^+$.

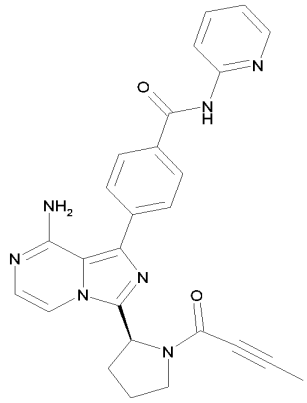
Example 5



(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 2-chloropyrimidine-4-carboxylic acid, to afford the title compound (8.3 mg, 40.4%). Data: UPLC (C) R_t : 1.64 min; *m/z* 540.1 $(M+H)^+$.

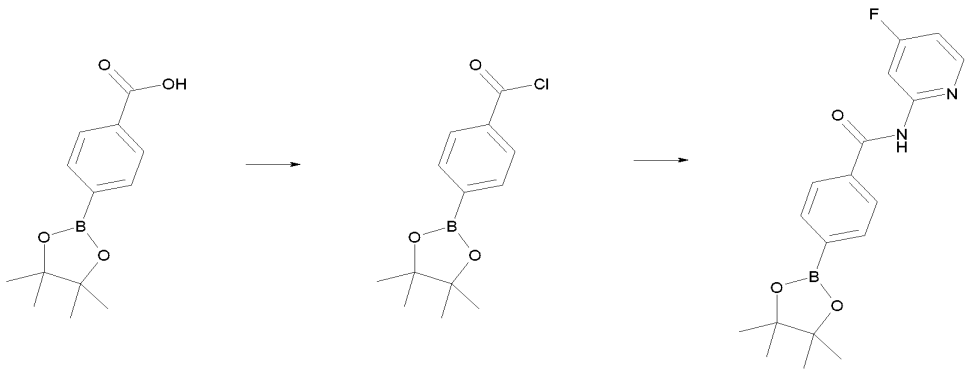
Example 6



(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 2-butynoic acid, to afford the title compound (10.5 mg, 18.0%). Data: LCMS (B) R_t : 2.08 min; *m/z* 466.1 $(M+H)^+$.

Intermediate 4



N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

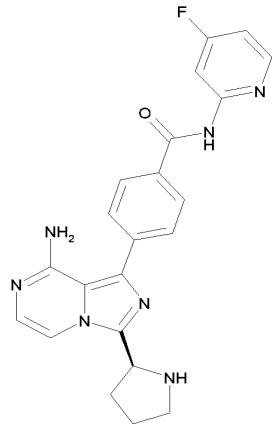
(a) 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride

To a cold (0°C) solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (40.3 mmol, 10.01 g) in dichloromethane (206 mL) was added a catalytic amount of DMF. A solution of oxalyl chloride (101 mmol, 8.66 mL, 12.8 g) was added drop wise. After stirring for 30 min at 0°C, the reaction mixture was allowed to warm up to room temperature and the mixture was stirred for an additional 3 hours. The reaction mixture was concentrated to give 10.9 g. of crude 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (101%).

(b) N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (1.688 mmol, 450 mg) in acetonitrile (24.8 mL) was added 2-amino-4-fluoropyridine (4.22 mmol, 473 mg). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated to a small volume, 3% aq. citric acid solution (18 mL) was added and the mixture was extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with 3% aq. citric acid solution, dried over magnesium sulfate, filtered and evaporated to afford 542.2 mg of N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (94%) as an off-white solid.

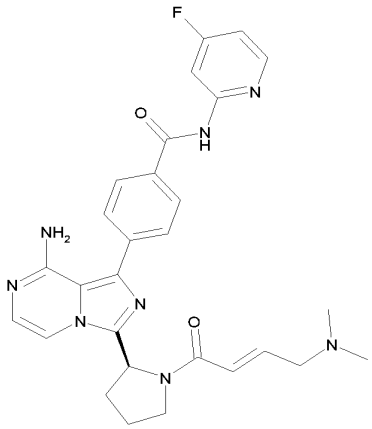
Intermediate 5



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2b, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 4b) to afford the title compound (331 mg, 93%).

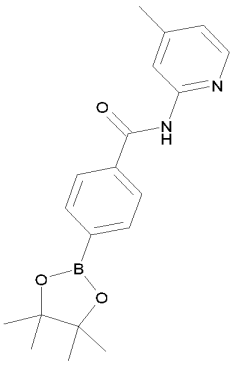
Example 7



(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 5 and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (33.4 mg, 54.1%). Data: UPLC (C) R_t : 1.72 min; *m/z* 529.3 $(M+H)^+$.

Intermediate 6

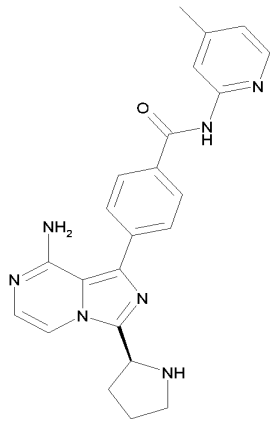


N-(4-Methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

To a stirred solution of 4-methylpyridin-2-amine (7.86 mmol, 850 mg) in THF (50 mL) was added dropwise a solution of 1M LiHMDS in THF (8.0 mmol, 8 mL) at room temperature. After the reaction mixture turned dark green, a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (9.6 mmol, 2.56 g) in dichloromethane (55 mL) was added dropwise. The

mixture was stirred at room temperature for 2.5 h and was then concentrated. 3% aq. Citric acid solution (18 mL) was added and the mixture was extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with 3% aq. citric acid solution, dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in THF (15 mL) and 6M NaOH solution (15 mL) was added. The mixture was stirred for 4 h. at room temperature. Ethyl acetate was added and the layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica (eluent: DCM/MeOH=98/2 to DCM/MeOH=95/5) to yield 1.1 g of N-(4-methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (40.7%).

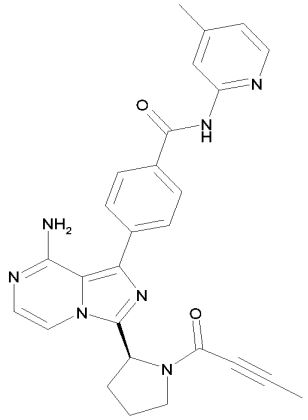
Intermediate 7



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 6) to afford the title compound (125.5 mg, 82%).

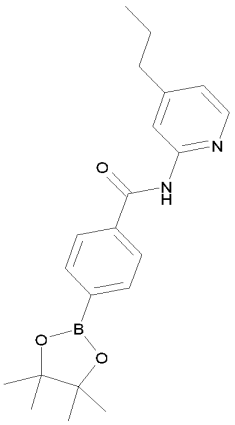
Example 8



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide (intermediate 7) and 2-butynoic acid, to afford the title compound (6.3 mg, 27.2%). Data: UPLC (C) R_t : 1.56 min; *m/z* 480.3 $(M+H)^+$.

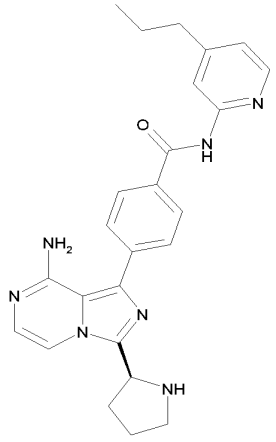
Intermediate 8



N-(4-Propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 6, starting from 4-propylpyridin-2-amine, to afford the title compound (371.5 mg, 54.1%).

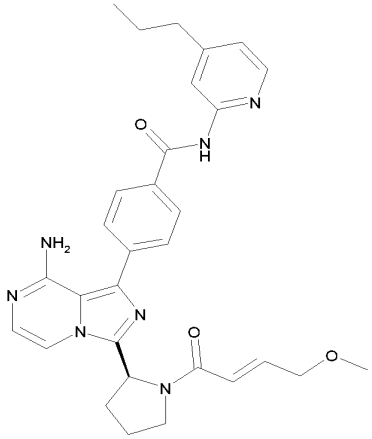
Intermediate 9



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-Propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 8) to afford the title compound (147.8 mg, 93%).

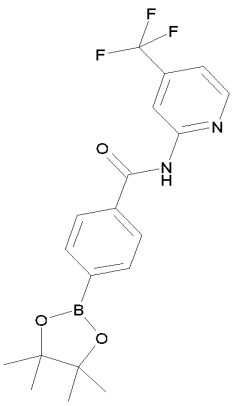
Example 9



(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide (intermediate 9) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (30.9 mg, 65.7%). Data: UPLC (C) R_t : 2.73 min; *m/z* 566.3 $(M+H)^+$.

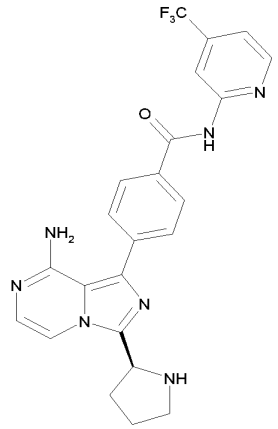
Intermediate 10



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 6, starting from 4-(trifluoromethyl)pyridin-2-amine, to afford the title compound (657.2 mg, 89%).

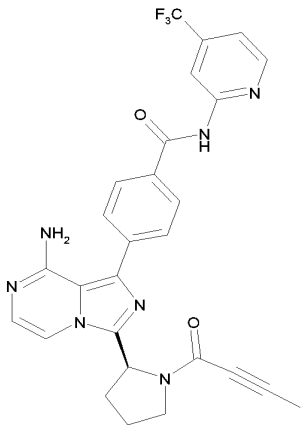
Intermediate 11



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 10) to afford the title compound (163 mg, 87%).

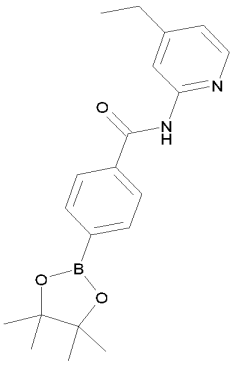
Example 10



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 11) and 2-butynoic acid, to afford the title compound (7.1 mg, 31.1%). Data: UPLC (C) R_t : 2.63 min; *m/z* 534.2 $(M+H)^+$.

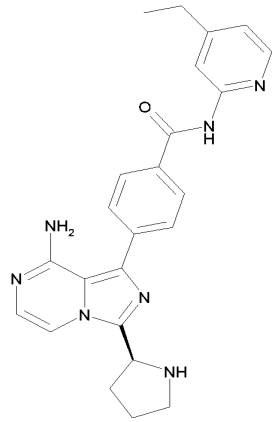
Intermediate 12



N-(4-Ethylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 4, starting from 4-ethylpyridin-2-amine, to afford the title compound (334.5 mg, 50.6%).

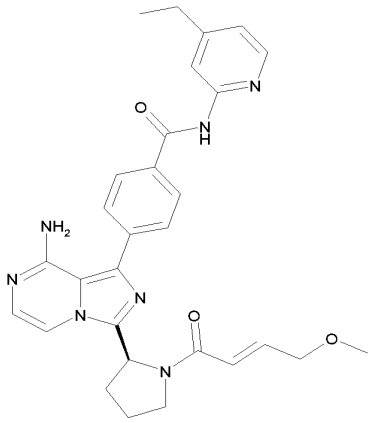
Intermediate 13



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-ethylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 12) to afford the title compound (133.8 mg, 89%).

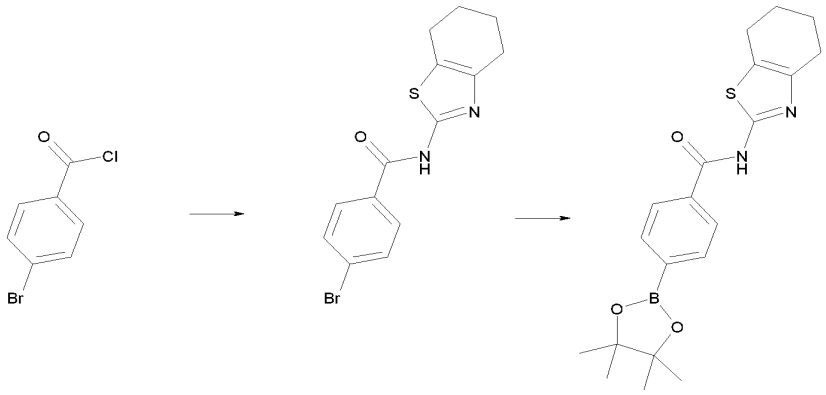
Example 11



(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide (intermediate 13) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (10.6 mg, 28.8%). Data: UPLC (C) R_t : 1.60 min; *m/z* 526.3 $(M+H)^+$.

Intermediate 14



N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

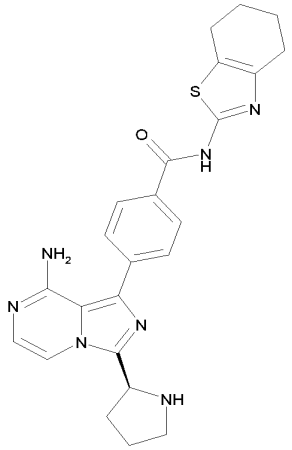
(a) 4-Bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

4-Bromobenzoyl chloride (1.5 g, 6.83 mmol) and 4,5,6,7-Tetrahydro-1,3-benzothiazol-2-amine (1.054 g, 6.83 mmol) were dissolved in Pyridine (15 ml) and stirred at 50°C for 1.5 h. The reaction mixture was cooled to room temperature and poured in water. The solid formed was filtered, washed with water. The solids were co-evaporated with toluene twice to afford 1.8 g of 4-bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (78%) as a yellow solid.

(b) N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)benzamide

To a solution of 4-bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (1.8 g, 5.34 mmol) dioxane (40 ml) was added bis(pinacolato)diboron (1.762 g, 6.94 mmol) and potassium acetate (1.048 g, 10.68 mmol). The reaction mixture was degassed with nitrogen. Subsequently 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.218 g, 0.267 mmol) added and the reaction mixture was stirred at 80°C for 5 days. The mixture was cooled to room temperature and after addition of water extracted three times with EtOAC. The organic layers were combined , washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified using silica gel chromatography (heptane/ethyl acetate 3/7 to 7/3 v/v%) to give 600 mg of N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)benzamide (29.3%).

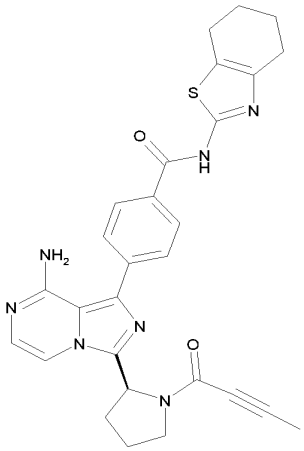
Intermediate 15



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 14b) to afford the title compound (260 mg, 60%).

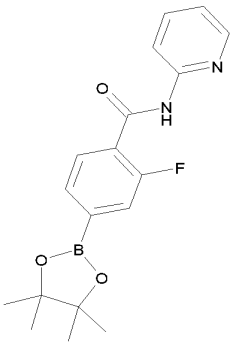
Example 12



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (intermediate 15) and 2-butynoic acid, to afford the title compound (7 mg, 19.2%). Data: UPLC (C) R_t : 2.41 min; *m/z* 526.3 $(M+H)^+$.

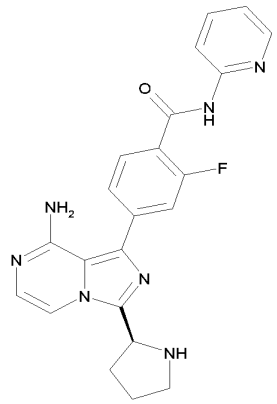
Intermediate 16



2-Fluoro-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 4-bromo-2-fluorobenzoic acid, to afford the title compound (2.54 g, 76%).

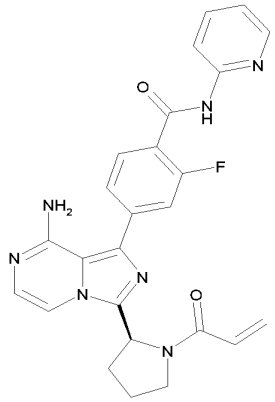
Intermediate 17



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 2-Fluoro-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 16) to afford the title compound (160 mg, 76%).

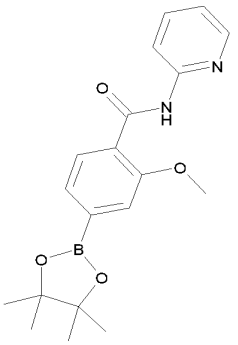
Example 13



(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide (intermediate 17) and acryloylchloride, to afford the title compound (13 mg, 38.4%). Data: UPLC (C) R_t : 1.67 min; *m/z* 472.3 $(M+H)^+$.

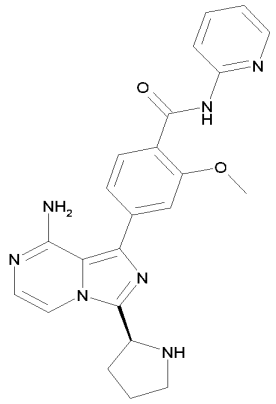
Intermediate 18



2-Methoxy-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 4-bromo-2-methoxybenzoic acid, to afford the title compound (2.6 g, 90%).

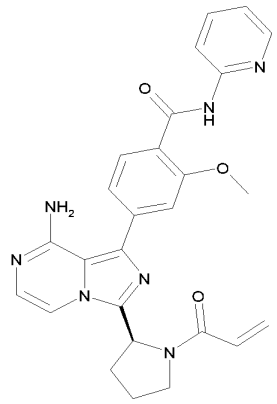
Intermediate 19



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 2-methoxy-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 18) to afford the title compound (175 mg, 56.6%).

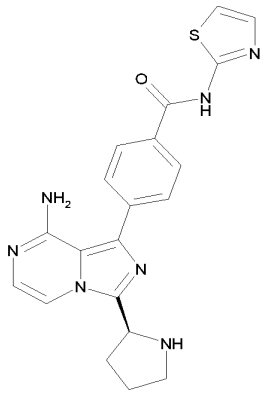
Example 14



(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide (intermediate 19) and acryloylchloride, to afford the title compound (14 mg, 35.5%). Data: UPLC (C) R_t : 1.74 min; *m/z* 484.3 $(M+H)^+$.

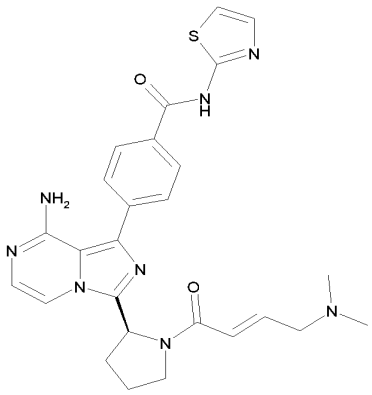
Intermediate 20



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and commercially available N-2-thiazolyl 4-boronobenzamide to afford the title compound (229 mg, 73.1%).

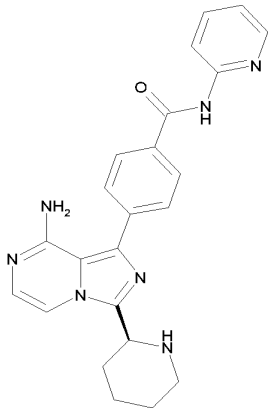
Example 15



(*S*,*E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide (intermediate 20) and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (18.9 mg, 29.7%). Data: UPLC (C) R_t : 1.38 min; *m/z* 517.3 $(M+H)^+$.

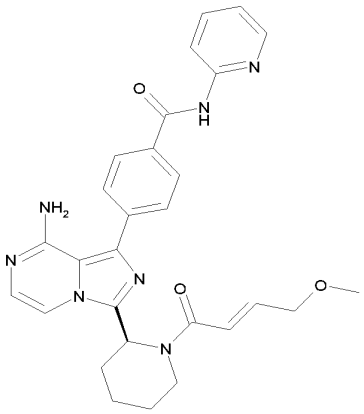
Intermediate 21



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, analogues as described for intermediate 2 afforded the title compound (491 mg, 91%).

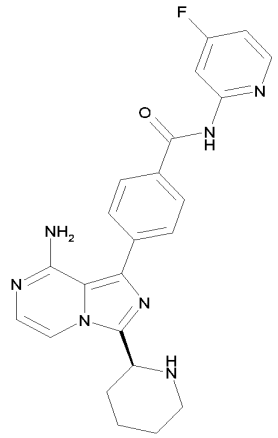
Example 16



(*S*,*E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 21) and (*E*)-4-methoxybut-2-enoic acid (intermediate 3), to afford the title compound (21.1 mg, 54.3%). Data: LCMS (B) R_t : 2.22 min; *m/z* 512.3 $(M+H)^+$.

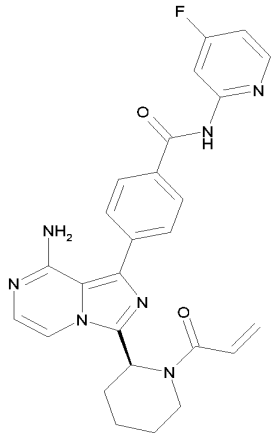
Intermediate 22



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 4), analogues as described for intermediate 2 afforded the title compound (160 mg, 71.8%).

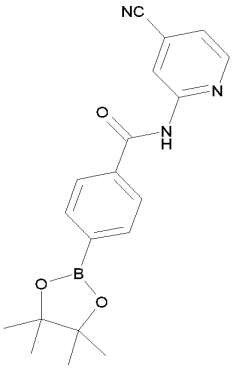
Example 17



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide (intermediate 22) and acryloylchlroide, to afford the title compound (12 mg, 42.7%). Data: UPLC(C) R_t : 2.29 min; *m/z* 486.3 $(M+H)^+$.

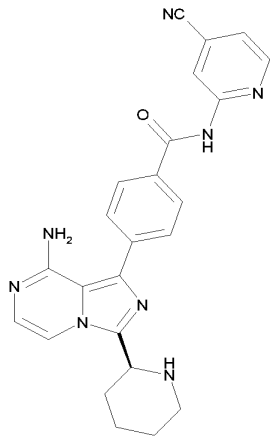
Intermediate 23



N-(4-Cyanopyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 4, starting from 2-aminoisonicotinonitrile, to afford the title compound (1.3 g, 99%).

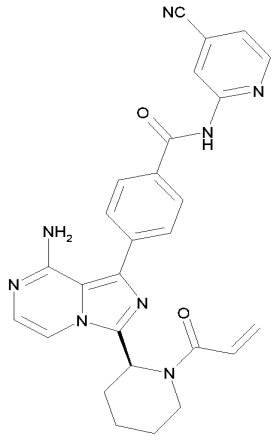
Intermediate 24



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-cyanopyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 23), analogues as described for intermediate 2 afforded the title compound (82 mg, 35.7%).

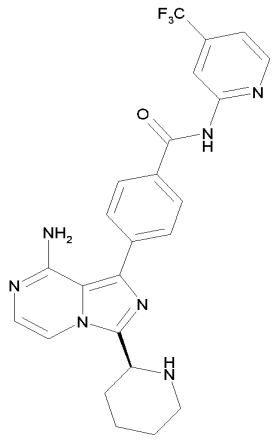
Example 18



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide (intermediate 24) and acryloylchloride, to afford the title compound (4.8 mg, 10.4%). Data: UPLC(C) R_t : 2.31 min.

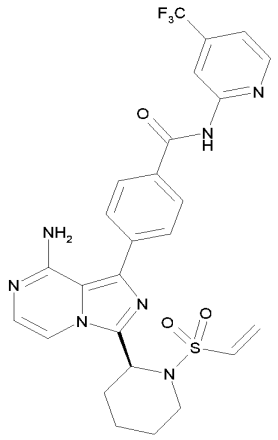
Intermediate 25



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (Intermediate 10), analogues as described for intermediate 2 afforded the title compound (144 mg, 59.1%).

Example 19

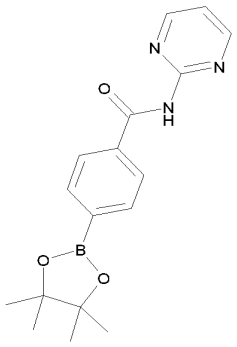


(*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 25) and ethenesulfonyl chloride prepared according to procedures

described by King et.al. in Can. J. Chem. **66** (1988) pp1109-1116, to afford the title compound (6.1 mg, 20.5%). Data: UPLC(B) R_t : 1.24 min; *m/z* 572.2 $(M+H)^+$.

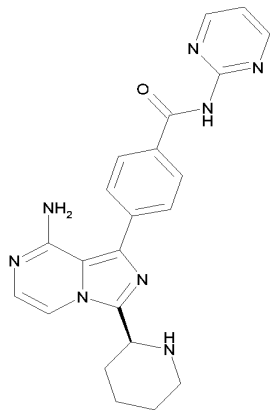
Intermediate 26



N-(Pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 2-aminopyrimidine, to afford the title compound (855 mg, 42.6%).

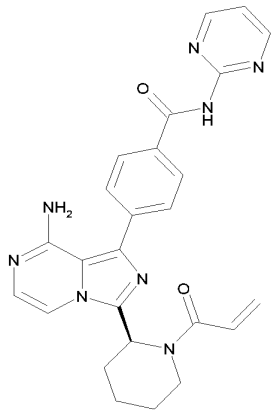
Intermediate 27



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 26), analogues as described for intermediate 2 afforded the title compound (100.8 mg, 95.4%).

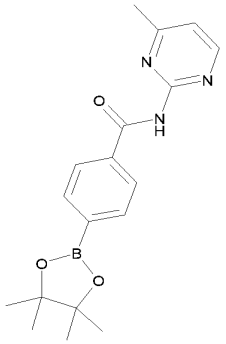
Example 20



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide (intermediate 27) and acryloylchloride, to afford the title compound (5.9 mg, 26.2%). Data: UPLC(C) R_t : 1.70 min; *m/z* 469.3 $(M+H)^+$.

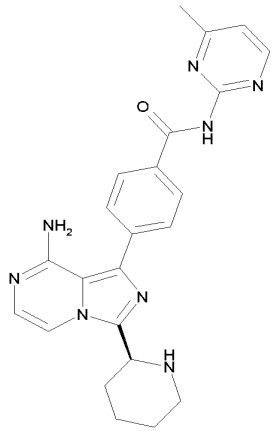
Intermediate 28



N-(4-Methylpyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 2-amino-4-methylpyrimidine, to afford the title compound (420 mg, 60.6%).

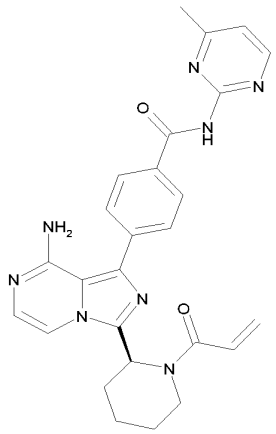
Intermediate 29



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-methylpyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 28), analogues as described for intermediate 2 afforded the title compound (83 mg, 50.4%).

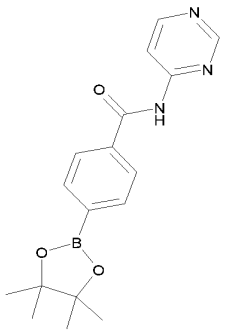
Example 21



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide (intermediate 29) and acryloylchloride, to afford the title compound (4.5 mg, 27.4%). Data: UPLC(C) R_t : 1.79 min; *m/z* 483.3 $(M+H)^+$.

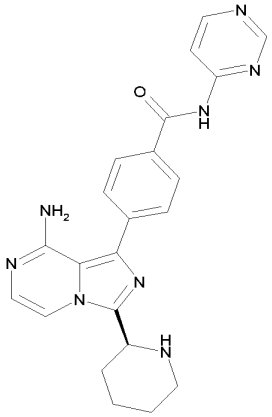
Intermediate 30



N-(Pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 4-aminopyrimidine, to afford the title compound (1 g, 59.4%).

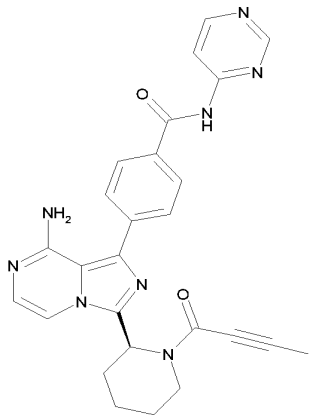
Intermediate 31



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 30), analogues as described for intermediate 2 afforded the title compound (66 mg, 42.8%).

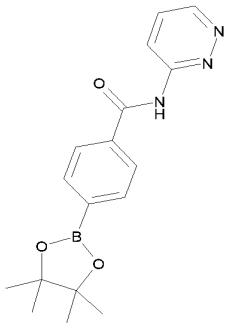
Example 22



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide (intermediate 31) and 2-butynoic acid, to afford the title compound (10.3 mg, 26.9%). Data: UPLC(C) R_t : 1.91 min; *m/z* 481.3 $(M+H)^+$.

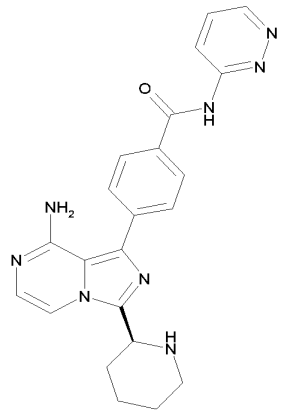
Intermediate 32



N-(Pyridazin-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 3-aminopyridazine, to afford the title compound (1.25 g, 71.3%).

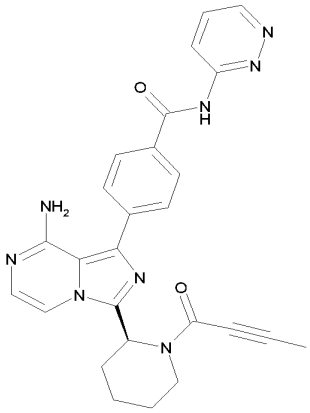
Intermediate 33



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyridazin-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 32) and deprotection, analogues as described for intermediate 2 afforded the title compound (258 mg, 85%).

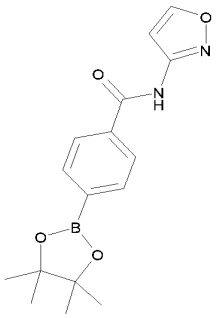
Example 23



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide (intermediate 33) and 2-butynoic acid, to afford the title compound (11 mg, 31.8%). Data: UPLC(C) R_t : 1.92 min; *m/z* 481.3 $(M+H)^+$.

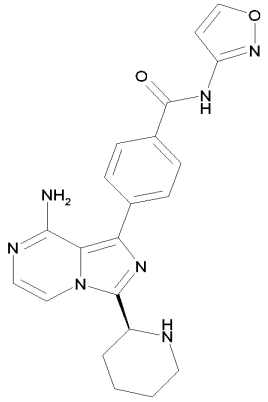
Intermediate 34



N-(Isoxazol-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from 3-aminoisoxazole, to afford the title compound (1.64 g, 95%).

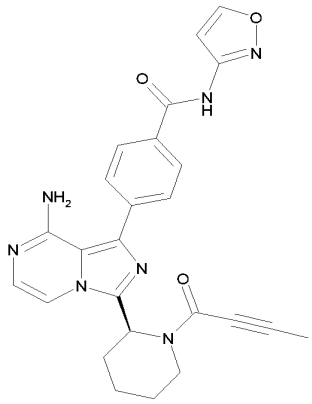
Intermediate 35



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(isoxazol-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 34) and deprotection, analogues as described for intermediate 2 afforded the title compound (72 mg, 129%).

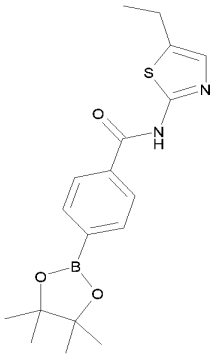
Example 24



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide (intermediate 35) and 2-butynoic acid, to afford the title compound (2 mg, 6.6%). Data: UPLC(C) R_t : 2.23 min; *m/z* 470.3 $(M+H)^+$.

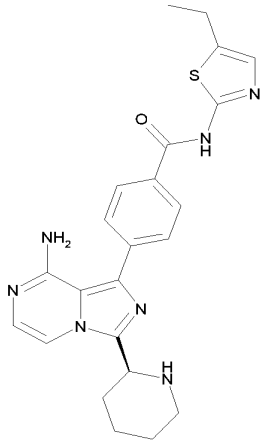
Intermediate 36



N-(5-Ethylthiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 4, starting from 5-ethylthiazol-2-amine, to afford the title compound (191 mg, 34.2%).

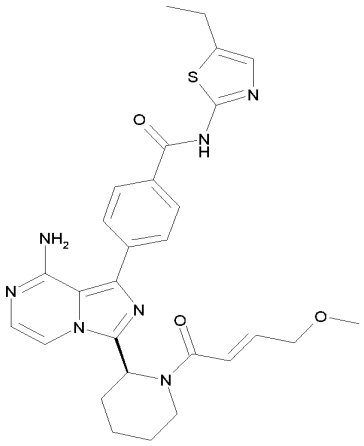
Intermediate 37



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(5-ethylthiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 36) and deprotection, analogues as described for intermediate 2 afforded the title compound (146 mg, 52.4%).

Example 25

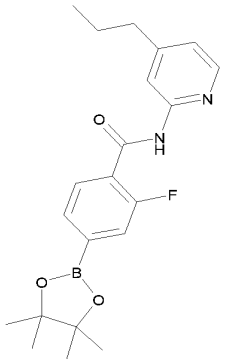


(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide

(intermediate 37) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (11.7 mg, 47.6%). Data: UPLC(C) R_t : 2.59 min; *m/z* 546.3 $(M+H)^+$.

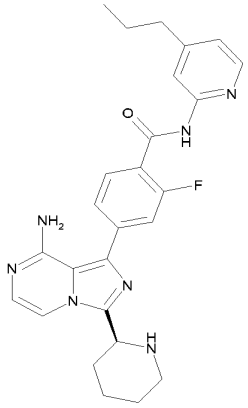
Intermediate 38



2-Fluoro-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 4, starting from commercially available 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid and 4-propyl-pyridin-2-ylamine, to afford the title compound (830 mg, 63.3%).

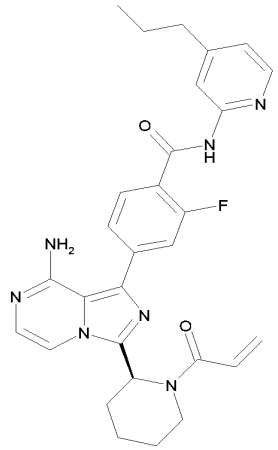
Intermediate 39



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 2-fluoro-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamid (Intermediate 38) and deprotection, analogues as described for intermediate 2 afforded the title compound (75.4 mg, 62%).

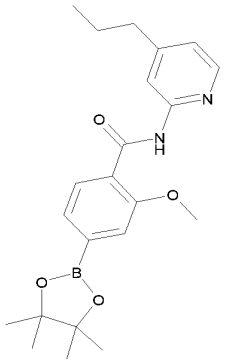
Example 26



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide (intermediate 39) and acrylic acid, to afford the title compound (5.9 mg, 28.9%). Data: UPLC(C) R_t : 2.41 min; *m/z* 528.4 $(M+H)^+$.

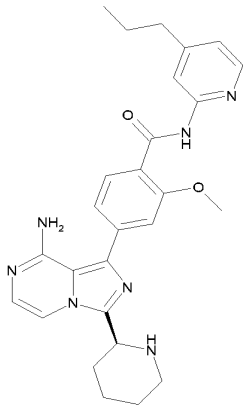
Intermediate 40



2-Methoxy-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from commercially available 4-bromo-2-methoxybenzoic acid and 4-propyl-pyridin-2-ylamine, to afford the title compound (240 mg, 15.1%).

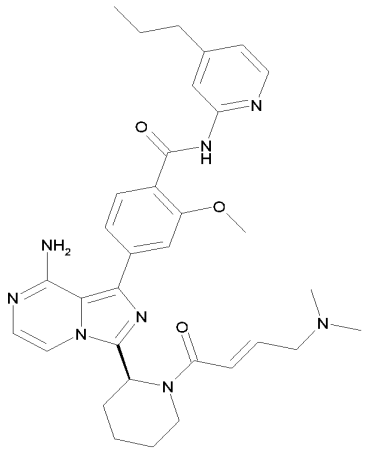
Intermediate 41



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 2-methoxy-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 40) and deprotection, analogues as described for intermediate 2 afforded the title compound (74.5 mg, 75%).

Example 27

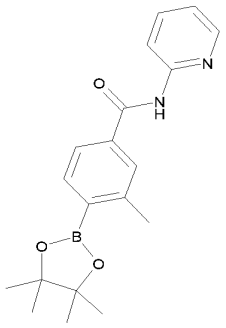


(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-

yl)benzamide (intermediate 41) and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (13.1 mg, 38.4%). Data: UPLC(C) R_t : 1.86 min; *m/z* 597.4 $(M+H)^+$.

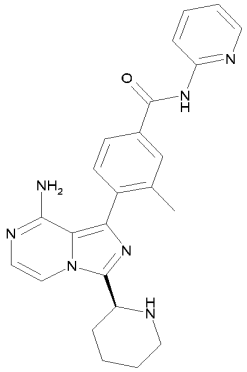
Intermediate 42



3-Methyl-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Intermediate 14, starting from commercially available 4-bromo-3-methylbenzoic acid and 2-aminopyridine, to afford the title compound (2.5 g, 71.3%).

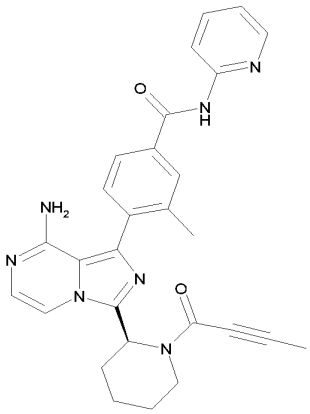
Intermediate 43



4-(8-Amino-3-((*S*)-piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 3-methyl-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 42) and deprotection, analogues as described for intermediate 2 afforded the title compound (150 mg, 71.7%).

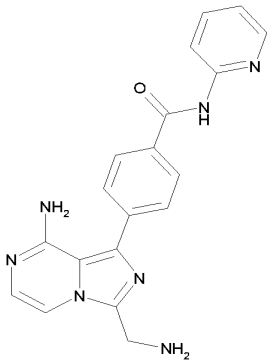
Example 28



4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from 4-(8-amino-3-((*S*)-piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide (intermediate 43) and 2-butynoic acid, to afford the title compound (13.7 mg, 59.1%). Data: UPLC(C) R_t : 2.28 min; *m/z* 494.3 $(M+H)^+$.

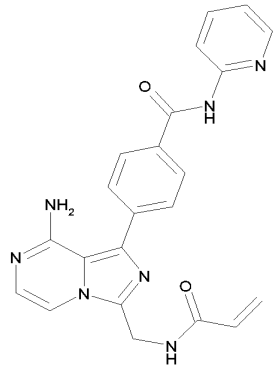
Intermediate 44



4-(8-Amino-3-(aminomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from Z-Gly-OH to obtain benzyl (8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)methylcarbamate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, analogues as described for intermediate 2 afforded the title compound (261 mg, 81%).

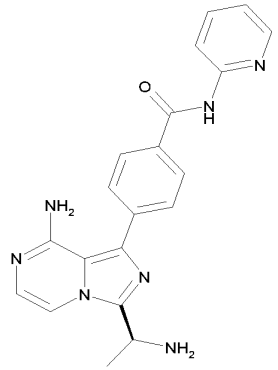
Example 29



4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from 4-(8-amino-3-(aminomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 44) and acryloylchloride, to afford the title compound (1.7 mg, 4%). Data: UPLC(C) R_t : 1.22 min; *m/z* 414.2 $(M+H)^+$.

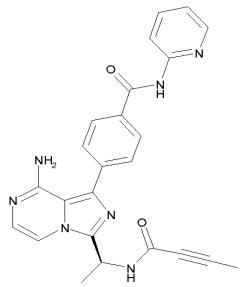
Intermediate 45



(*S*)-4-(8-Amino-3-(1-aminoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from Z-Ala-OH to obtain benzyl (*S*)-benzyl 1-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)ethylcarbamate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid and deprotection with 33%HBr/HOAc, analogues as described for intermediate 2 afforded the title compound (133.6 mg, 80%).

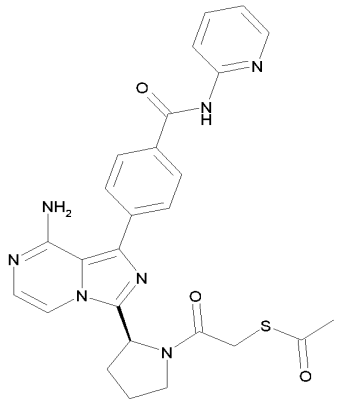
Example 30



(*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(1-aminoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 45) and 2-butynoic acid, to afford the title compound (9.5 mg, 26.9%). Data: UPLC(C) R_t : 1.38 min; *m/z* 440.3 $(M+H)^+$.

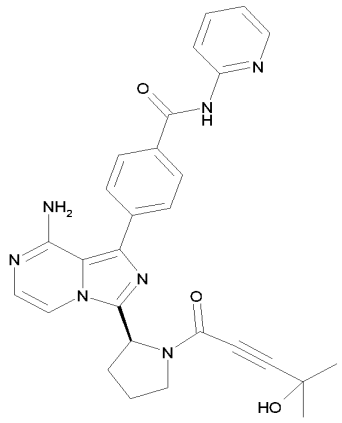
Example 31



(*S*)-S-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate

This compound was prepared, in an analogues manner as described in Example 1, from the compound described in intermediate 2b and 2,5-dioxopyrrolidin-1-yl 2-(acetylthio)acetate, to afford the title compound (12.3 mg, 31.8%). Data: UPLC (C) R_t : 1.51 min; *m/z* 516.3 $(M+H)^+$.

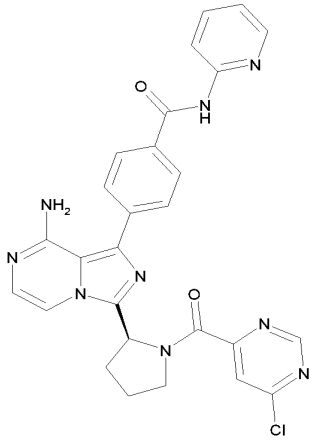
Example 32



(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 4-hydroxy-4-methylpent-2-ynoic acid, to afford the title compound (8.0 mg, 25.1%). Data: UPLC (C) R_t : 1.53 min; *m/z* 510.3 $(M+H)^+$.

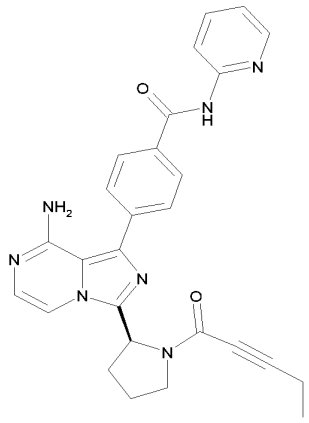
Example 33



(*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 6-chloropyrimidine-4-carboxylic acid, to afford the title compound (2.5 mg, 6.2%). Data: UPLC (C) R_t : 1.64 min; *m/z* 540.3 $(M+H)^+$.

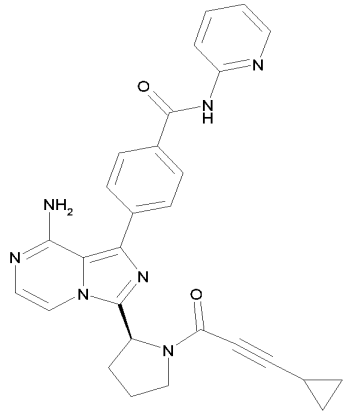
Example 34



(*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and pent-2-ynoic acid, to afford the title compound (7.4 mg, 24.7%). Data: UPLC (C) R_t : 1.73 min; *m/z* 480.3 $(M+H)^+$.

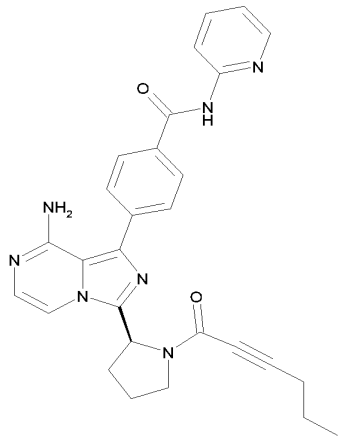
Example 35



(*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 3-cyclopropylpropiolic acid, to afford the title compound (8 mg, 26%). Data: UPLC (C) R_t : 1.73 min; *m/z* 492.3 $(M+H)^+$.

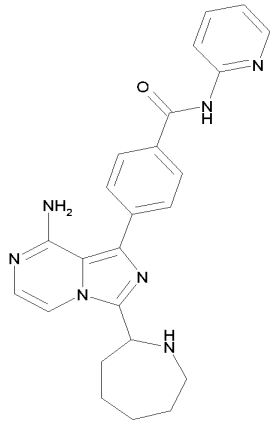
Example 36



(*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and hex-2-ynoic acid, to afford the title compound (8.1 mg, 26.2%). Data: UPLC (C) R_t : 1.94 min; *m/z* 494.3 $(M+H)^+$.

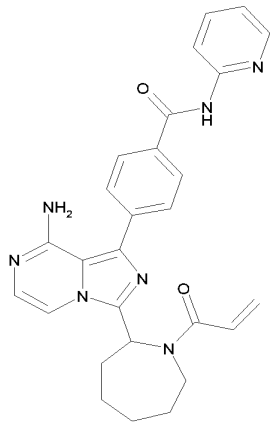
Intermediate 46



4-(8-Amino-3-(azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from 1-(benzyloxycarbonyl)azepane-2-carboxylic acid to obtain benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)azepane-1-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, analogues as described for intermediate 2 afforded the title compound (436 mg, quantitative, crude).

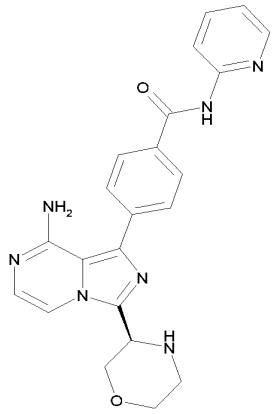
Example 37



4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 1, from 4-(8-amino-3-(azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 46) and acryloylchloride, to afford the title compound (11 mg, 32.6%). Data: UPLC(C) R_t : 1.88 min; *m/z* 482.3 $(M+H)^+$.

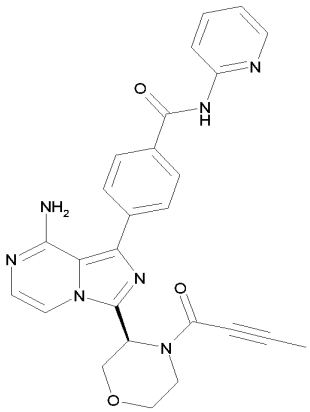
Intermediate 47



(*R*)-4-(8-Amino-3-(morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-4-(benzyloxycarbonyl)morpholine-3-carboxylic acid to obtain (*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)morpholine-4-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, analogues as described for intermediate 2 and subsequent deprotection using TFA at 60°C, afforded the title compound (62 mg, 69.5%).

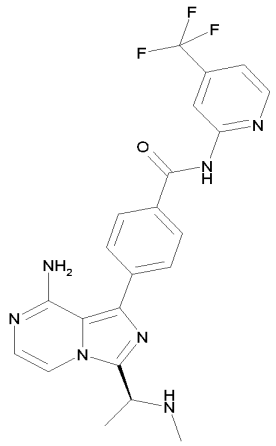
Example 38



(*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogues manner as described in Example 2, from (*R*)-4-(8-amino-3-(morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 47) and 2-butynoic acid, to afford the title compound (4.9 mg, 14.1%). Data: UPLC(C) R_t : 1.38 min; *m/z* 482.3 $(M+H)^+$.

Intermediate 48

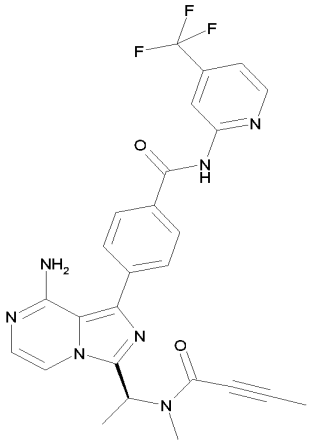


(*S*)-4-(8-Amino-3-(1-(methylamino)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogues manner as described for intermediate 1, from (*S*)-2-((benzyloxycarbonyl)(methyl)amino)propanoic acid to obtain (*S*)-benzyl 1-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)ethyl(methyl)carbamate. Subsequent reaction with 4-(4,4,5,5-

Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (Intermediate 10), analogues as described for intermediate 2 afforded the title compound (71 mg, 64.7%).

Example 39



(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

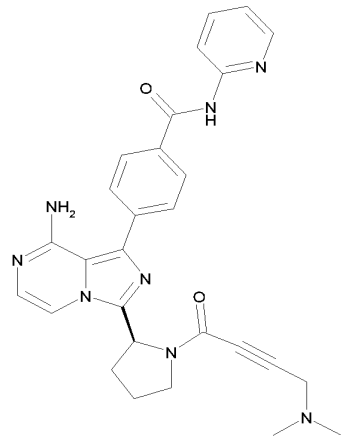
This compound was prepared, in an analogues manner as described in Example 2, from (*S*)-4-(8-amino-3-(1-(methylamino)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 48) and 2-butynoic acid, to afford the title compound (11.5 mg, 33.4%). Data: UPLC(C) R_t : 2.54 min; *m/z* 522.2 $(M+H)^+$.

Intermediate 49

4-(Dimethylamino)but-2-ynoic acid

n-BuLi in hexane (2.5M, 24.06 mmol, 9.62 mL) was slowly added to a solution of *N,N*-dimethylprop-2-yn-1-amine (24.06 mmol, 2,59 mL, 2 g) in dry THF (10 mL) at -78°C. The mixture was stirred for 1 h at -78°C, then crushed CO_2 (241 mmol, 10.59 g) was added in one portion and the reaction mixture was stirred for an additional 10 min. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated *in vacuo* to give the crude amino acid. This was dissolved in methanol, and the insoluble salts were removed via filtration. The filtrate was evaporated to give 3.25 g of 4-(dimethylamino)but-2-ynoic acid (106%).

Example 40



(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

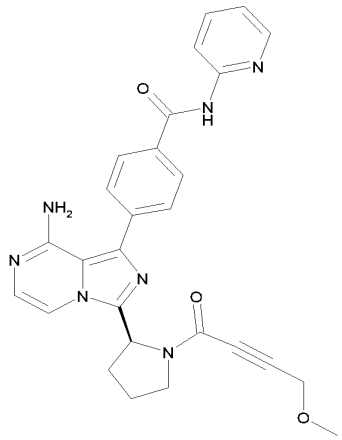
This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 4-(dimethylamino)but-2-ynoic acid (Intermediate 49), to afford the title compound (5.6 mg, 12%). Data: UPLC (C) R_t : 0.97 min; *m/z* 509.3 $(M+H)^+$.

Intermediate 50

4-Methoxybut-2-ynoic acid

n-BuLi in hexane (2.5M, 28.5 mmol, 11.41 mL) was slowly added to a solution of 3-methoxyprop-1-yne (28.5 mmol, 2,41 mL, 2 g) in dry THF (10 mL) at -78°C. The mixture was stirred for 1 h at -78°C, then crushed CO_2 (285 mmol, 12.56 g) was added in one portion and the reaction mixture was stirred for an additional 10 min. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated *in vacuo* to give the crude amino acid. This was dissolved in methanol, and the insoluble salts were removed via filtration. The filtrate was evaporated to give 3.35 g of 4-methoxybut-2-ynoic acid (103%).

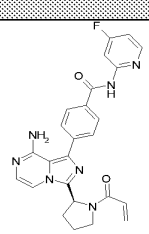
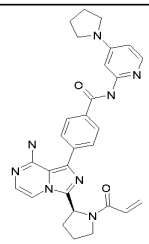
Example 41

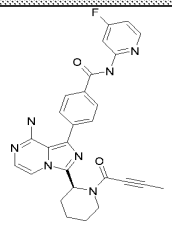
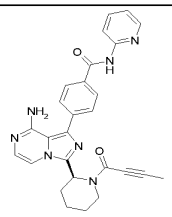
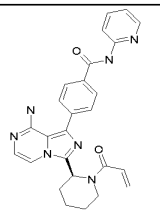
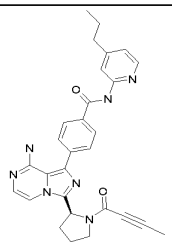
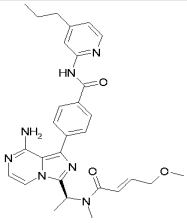
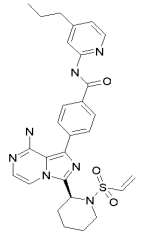


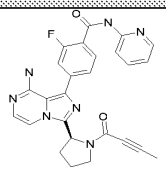
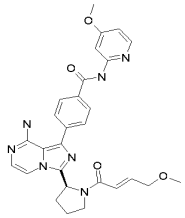
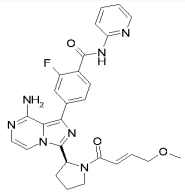
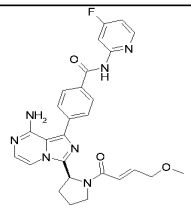
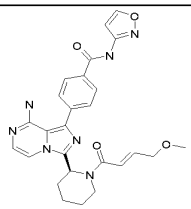
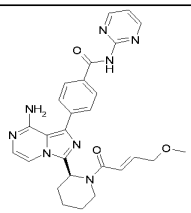
(*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

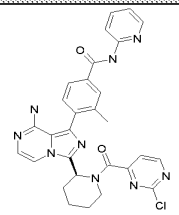
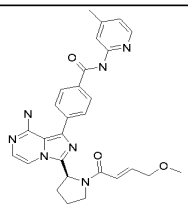
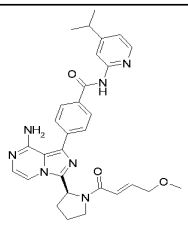
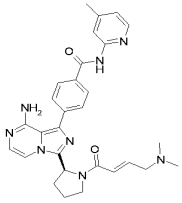
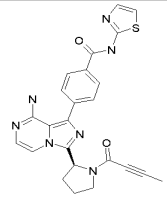
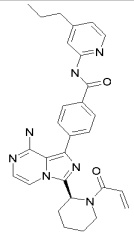
This compound was prepared, in an analogues manner as described in Example 2, from the compound described in intermediate 2b and 4-methoxybut-2-ynoic acid (Intermediate 50), to afford the title compound (9.1 mg, 24.7%). Data: UPLC (C) R_t : 1.44 min; *m/z* 496.2 $(M+H)^+$.

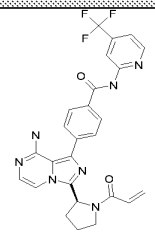
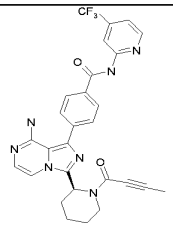
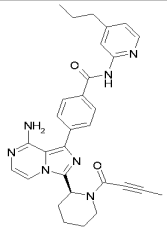
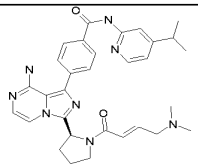
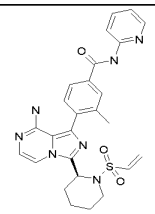
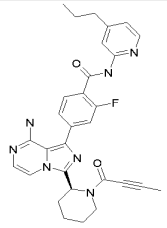
The following Examples were synthesized following the methods described for example 1-41.

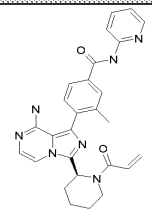
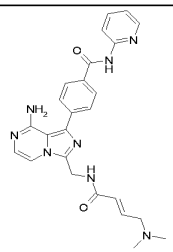
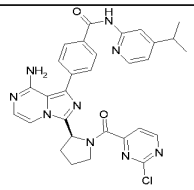
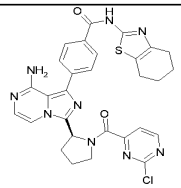
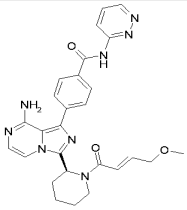
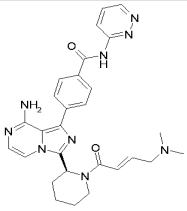
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
42		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	472.3	2.25 min
43		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide	523.3	1.72 min

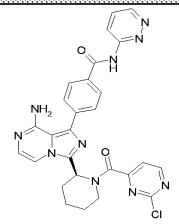
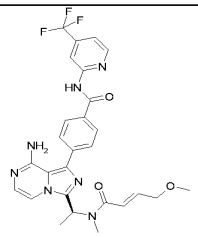
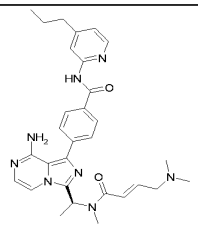
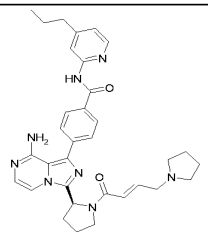
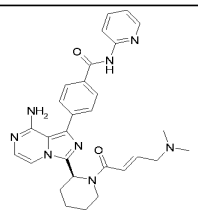
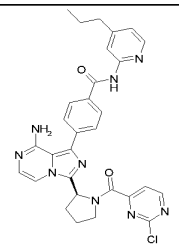
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
44		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	498.3	2.47 min
45		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	480.3	2.26 min LCMS (B)
46		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.3	2.49 min
47		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	508.3	2.00 min
48		(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	528.3	1.89 min
49		(*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	546.3	2.15 min

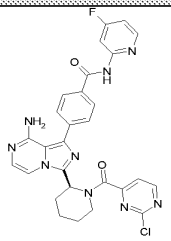
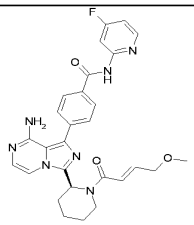
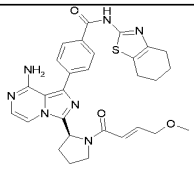
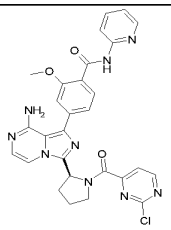
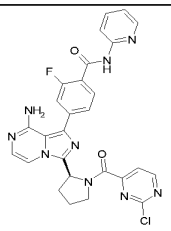
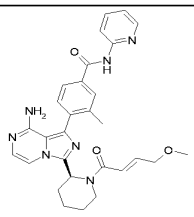
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
50		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide	484.3	1.84 min
51		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide	528.4	1.60 min
52		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-methoxypyridin-2-yl)benzamide	516.3	1.79 min
53		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	516.3	2.31 min
54		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide	502.3	2.01 min
55		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide	513.3	1.79 min

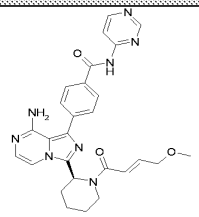
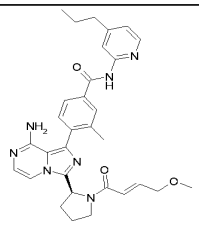
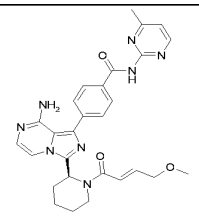
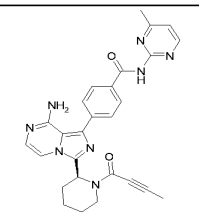
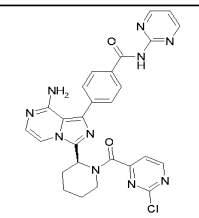
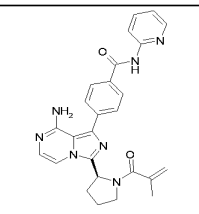
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
56		4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	568.3	2.23 min
57		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	512.4	1.67 min
58		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	540.3	1.74 min
59		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	525.4	1.11 min
60		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	472.0	2.24 min
61		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	510.3	2.11 min

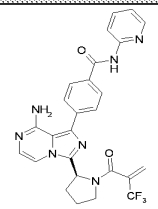
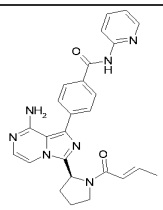
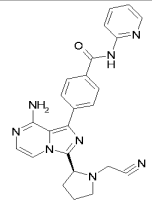
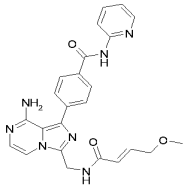
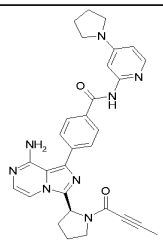
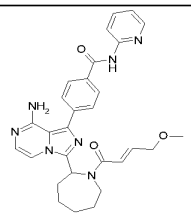
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
62		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	522.0	2.37 min
63		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	548.3	1.09 min UPLC (B)
64		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	522.3	2.29 min
65		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	553.3	1.31 min
66		4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	518.3	2.20 min
67		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	540.3	2.56 min

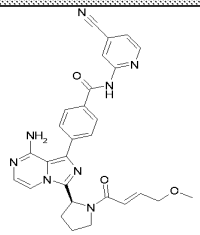
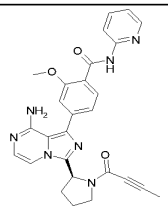
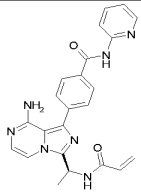
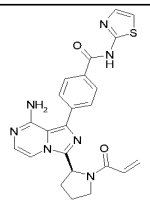
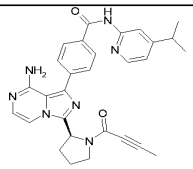
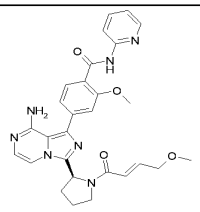
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
68		4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	482.2	1.98 min
69		(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl) imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	471.2	1.16 min
70		(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	582.2	1.89 min
71		(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	600.2	2.49 min
72		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	513.3	1.84 min
73		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	526.4	1.26 min

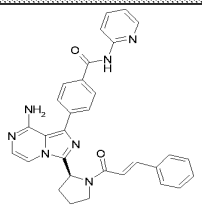
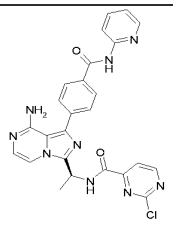
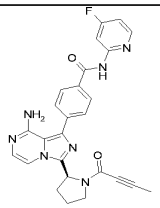
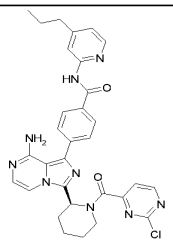
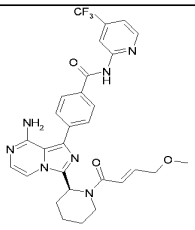
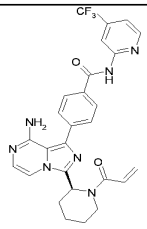
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
74		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	555.3	1.96 min
75		(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	554.2	2.47 min
76		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	541.3	1.41 min
77		(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	579.3	1.64 min
78		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	525.3	2.10 min LCMS (B)
79		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	582.3	1.95 min

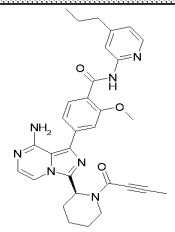
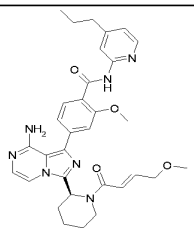
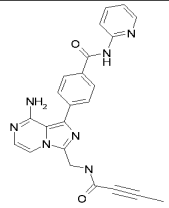
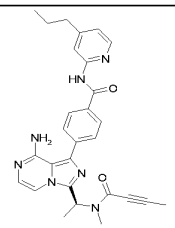
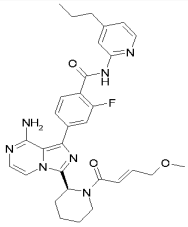
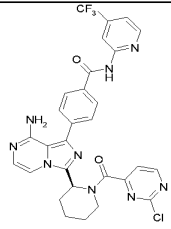
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
80		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	572.3	2.45 min
81		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	530.3	2.38 min
82		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	558.3	2.33 min
83		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	570.3	2.01 min
84		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide	558.2	1.95 min
85		4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	526.3	2.12 min

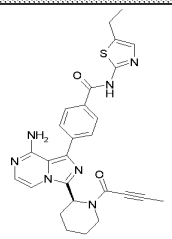
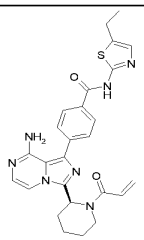
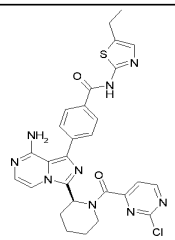
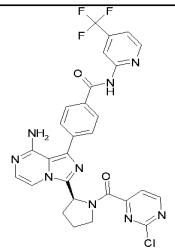
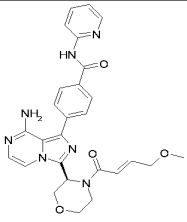
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
86		(*S*,*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide	513.3	1.83 min
87		4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide	554.4	1.86 min
88		(*S*,*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide	527.3	1.88 min
89		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide	495.3	1.97 min
90		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide	555.3	1.91 min
91		(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.4	1.61 min

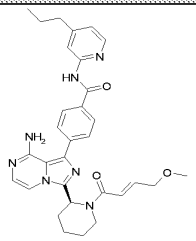
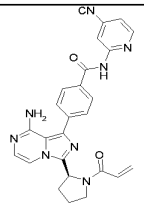
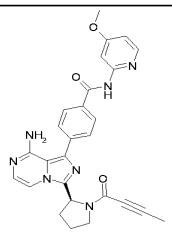
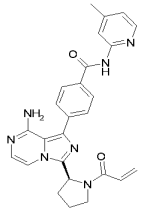
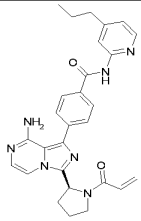
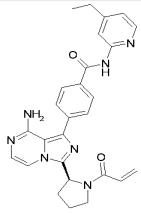
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
92		(*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	522.3	1.99 min
93		(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.4	1.59 min
94		(*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	439.3	1.55 min
95		(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	458.2	1.35 min
96		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide	535.3	2.27 min LCMS (B)
97		(*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	526.3	1.97 min

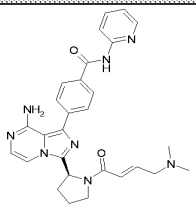
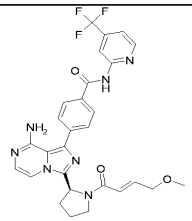
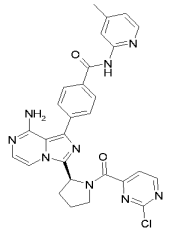
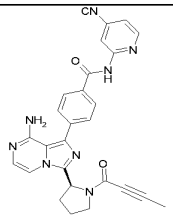
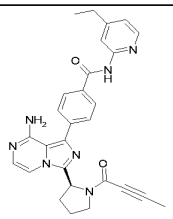
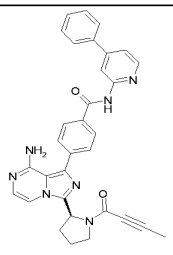
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
98		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	523.3	2.12 min
99		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	496.3	1.87 min
100		(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	428.3	1.15 min
101		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	460.2	2.03 min
102		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	507.8	1.82 min
103		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	528.3	1.84 min

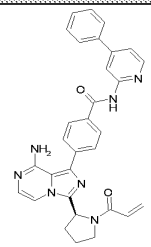
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
104		(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	530.4	2.09 min
105		(*S*)-N-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide	514.3	1.56 min
106		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	484.2	2.38 min
107		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	596.3	2.19 min
108		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	580.3	1.03 min UPLC (B)
109		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	536.3	1.02 min UPLC (B)

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
110		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	552.4	2.57 min
111		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	584.4	2.49 min
112		4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	426.2	1.35 min
113		(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	496.3	1.94 min
114		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	572.4	2.48 min
115		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	622.2	1.15 min UPLC (B)

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
116		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	514.3	2.68 min
117		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	502.3	2.53 min
118		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	588.3	2.71 min
119		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	608.2	2.68 min
120		(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	514.3	1.34 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
121		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	554.4	2.07 min
122		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	479.0	1.86 min
123		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide	496.3	1.50 min
124		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	468.1	1.37 min
125		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	496.1	1.76 min
126		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	482.1	1.53 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
127		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	511.0	1.29 min
128		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	566.3	2.73 min
129		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	554.2	1.38 min
130		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	491.2	2.20 min
131		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	494.3	1.65 min
132		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	542.3	2.57 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
133		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	530.3	2.38 min

Example 134 Assay Methods

Btk enzyme activity

Btk enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Btk enzyme (His-Btk (Millipore catalog# 14-552), is diluted to 0.4 U/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer. Final compound concentration range in the assay from 10 μM to 0.316 nM.

5 μL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 μl/well of 0.4 U/mL Btk enzyme (final concentration in the assay is 0.1 U/mL). Test compounds and Btk enzyme are pre-incubated 60 minutes at room temperature, before adding 5 μL/well of 200 nM Fluorescin labeled substrate peptide (Blk/Lyntide substrate, e.g. #R7188/#R7233, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 50 nM. The kinase assay is started by adding 5 μL/well of 20 μM ATP in KR-buffer (final ATP concentration is 5 μM ATP, Km ATP in Btk IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 μL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

All examples have an EC50 of 10 μM or lower.

Table 1 EC50 Btk activity values	
EC50	**Example**
≥1μM	91,
≥100nM <1μM	52, 53, 54, 55, 68, 72, 74, 85, 86, 87, 88, 90, 92, 93, 94, 104
≥10nM <100nM	2, 4, 5, 7, 11, 24, 40, 41, 50, 51, 56, 57, 58, 59, 60, 69, 70, 71, 73, 80, 81, 82, 83, 84, 89, 95, 96, 97, 98, 99, 103, 105, 106, 112, 113, 114, 119
<10 nM	1, 3, 6, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 61, 62, 63, 64, 65, 66, 67, 75, 76, 77, 78, 79, 100, 101, 102, 107, 108, 109, 110, 111, 115, 116, 117, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

Lck enzyme activity

Lck enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Lck enzyme (Millipore catalog# 14-442), is diluted to 0.4 U/mL in KR buffer (10 mM Tris-HCl, 10 mM MgCl2, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 µl is used in the assay, leading to a final compound concentration range in the assay from 10 µM to 0.316 nM.

5 µL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 µl/well of 0.4 U/mL Lck enzyme (final concentration in the assay is 0.1 U/mL). Test compounds and Lck enzyme are pre-incubated 60 minutes at room temperature, before adding 5 µL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 µL/well of 24 µM ATP in KR-buffer (final ATP concentration is 6 µM ATP, Km ATP in Lck IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 µL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 2 EC50 Lck activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 123, 127, 128, 129, 130, 131
≥100nM <1μM	60, 62, 64, 76, 104, 122, 124, 125, 126, 132, 133

Src enzyme activity

Src enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Src enzyme (Millipore catalog# 14-326), is diluted to 0.8 U/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 μl is used in the assay, leading to a final compound concentration range in the assay from 10 μM to 0.316 nM.

5 μL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 μl/well of 0.8 U/mL Src enzyme (final concentration in the assay is 0.2 U/mL). Test compounds and Src enzyme are pre-incubated 60 minutes at room temperature, before adding 5 μL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 μL/well of 16 μM ATP in KR-buffer (final ATP concentration is 4 μM ATP, Km ATP in Src IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 μL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 3 EC50 Src activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

FynT enzyme activity

FynT enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

FynT enzyme (Biomol catalog# SE-287), is diluted to 0.5 μg/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 μl is used in the assay, leading to a final compound concentration range in the assay from 10 μM to 0.316 nM.

5 μL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 μl/well of 0.5 μg/mL FynT enzyme (final concentration in the assay is 125 ng/mL). Test compounds and FynT enzyme are pre-incubated 60 minutes at room temperature, before adding 5 μL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 μL/well of 0.8 μM ATP in KR-buffer (final ATP concentration is 0.2 μM ATP, Km ATP in FynT IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 μL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 4 EC50 FynT activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

Lyn enzyme activity

Lyn enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Lyn enzyme (Millipore catalog# 14-510), is diluted to 250 mU/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

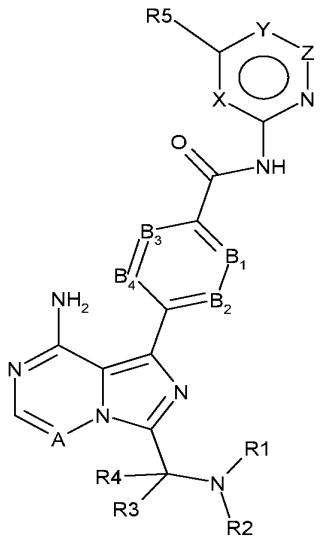
Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 µl is used in the assay, leading to a final compound concentration range in the assay from 10 µM to 0.316 nM.

5 µL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 µl/well of 250 mU/mL Lyn enzyme (final concentration in the assay is 62.5 mU/mL). Test compounds and Lyn enzyme are pre-incubated 60 minutes at room temperature, before adding 5 µL/well of 400 nM Fluorescin labeled substrate peptide (Blk/Lyntide substrate, e.g. #R7188/#R7233, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 µL/well of 8 µM ATP in KR-buffer (final ATP concentration is 2 µM ATP, Km ATP in Lyn IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 µL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 5 EC50 Lyn activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 127, 128, 129, 130, 131, 132
≥100nM <1μM	60, 124, 125, 126, 133

Claims

1. Compound according to formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO_2 or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, halogen or (1-3C)alkoxy;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the carbon atom they are attached to a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, halogen or (1-3C)alkoxy

R10 is H, halogen or (1-3C)alkoxy

R11 is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R12 and R13 are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;
- when Z is C or N then Y is C(R6) or N and X is C or N;
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

2. The compound according to claim 1 wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10);

R7, R9, and R10 each are H; and

R8 is selected from a group consisting of hydrogen and methyl.

3. The compound according to anyone of claims 1 to 2 wherein R4 is selected from a group consisting of hydrogen and methyl.

4. The compound according to anyone of claims 1 to 3 wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl, and isoxazolyl.
5. The compound according to anyone of claims 1 to 4 wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl, and thiazolyl.
6. The compound according to anyone of claims 1 to 5 wherein R5 is selected from a group consisting of hydrogen, fluorine, chlorine, (1-3C)alkyl and (1-2C) alkoxy; the (1-3C)alkyl group of which is optionally substituted with one or more halogen.
7. The compound according to anyone of claims 1 to 6 wherein R5 is selected from a group consisting of hydrogen, fluorine, methyl, ethyl, propyl, methoxy and trifluoromethyl.
8. The compound according to anyone of claims 1 to 7 wherein R2 is hydrogen or (1-3C)alkyl; and R3 is (1-6C)alkyl.
9. The compound according to anyone of claims 1 to 7 wherein R2 and R3 together form a heterocycloalkyl ring selected from azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl, optionally substituted with one or more fluoro, hydroxyl, (1-3C) alkyl, (1-3C)alkoxy, or oxo.
10. The compound according to anyone of claims 1 to 9 wherein R1 is R11C(O) and R11 is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl each optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.
11. The compound according to anyone of claims 1 to 10 wherein R1 is R11C(O) and R11 is selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl each optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy or (3-7C)heterocycloalkyl.
12. Compound according to claim 1 selected from a group consisting of
(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide;

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;

(*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide ;

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide ;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide ;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide ;

(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide ;

(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide;

(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide;
4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;
4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-S-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate;
(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide ;
(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-methoxypyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide;
4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide;

4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide;

4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;

(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl) imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide;

4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide;

4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide;

(*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide;

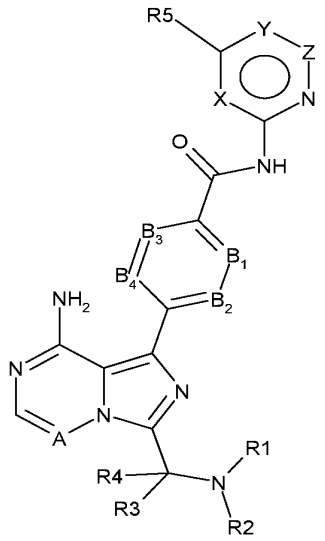
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-N-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide;
4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide;
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide;
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide;
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide and
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide.

13. The compound of anyone of claim 1 to 12 for use in therapy.
14. The compound of anyone of claim 1 to 12 for use in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.
15. Use of a compound of formula I according to any of the claims 1 to 12 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

Abstract;

The present invention relates to 6-5 membered fused pyridine ring compounds according to formula I



Formula I

or a pharmaceutically acceptable salt thereof or to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds according to formula I in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/019,543	02/09/2016	1629	1740	015332.1182-US02	19	2

CONFIRMATION NO. 1984

FILING RECEIPT

26853
COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

OC000000080871519

Date Mailed: 02/25/2016

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

Inventor(s)

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Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a DIV of 14/233,418 01/17/2014
which is a 371 of PCT/EP2012/063552 07/11/2012
which claims benefit of 61/509,397 07/19/2011

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
EUROPEAN PATENT OFFICE (EPO) 11174578.2 07/19/2011

Permission to Access Application via Priority Document Exchange: No

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Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

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

If Required, Foreign Filing License Granted: 02/24/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/019,543**

Projected Publication Date: 06/02/2016

Non-Publication Request: No

Early Publication Request: No

Title

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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

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

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

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/019,543

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/019,543	02/09/2016	Tjeerd A. Barf	015332.1182-US02

CONFIRMATION NO. 1984

26853
COVINGTON & BURLING, LLP
Attn: Patent Docketing
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956

INFORMAL NOTICE

OC000000080871520

Date Mailed: 02/25/2016

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Tjeerd A. Barf
  Christiaan Gerardus Johannes Maria Jans
  Petrus Antonius de Adrianu Man
  Arthur A. Oubrie
  Hans C. A. Raaijmakers
  Johannes Bernardus Maria Rewinkel
  Jan-Gerard Sterrenburg
  Jacobus C. H. M. Wijkmans

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mabebe/

PTO/AIA/15 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	015332.1182-US02
First Named Inventor	Tjeerd A. Barf
Title	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] **Specification** [*Total Pages* 109]
   Both the claims and abstract must start on a new page.
   (See MPEP § 608.01(a) for information on the preferred arrangement)
5. [ ] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets*]
6. **Inventor's Oath or Declaration** [*Total Pages*]
   (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [X] **Application Data Sheet** ** See note below.*
   See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

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

ACCOMPANYING APPLICATION PAPERS

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

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 26853 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature		Date	February 9, 2016
Name (Print/Type)	Melody H. Wu	Registration No. (Attorney/Agent)	52,376

DC: 5968009-1

4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK-INHIBITORS

Related applications

This application is a divisional of U.S. Patent Application No. 14/233,418, which is the U.S. national stage of International Patent Application No. PCT/EP2012/063552 filed July 11, 2012, which claims priority to U.S. Patent Application No. 61/509,397 filed July 19, 2011, and to EP Patent Application No. 11174578.2 filed July 19, 2011, each of which is hereby incorporated by reference in its entirety herein.

Field of the invention

The present invention relates to 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

Background of the invention

B lymphocyte activation is key in the generation of adaptive immune responses. Derailed B lymphocyte activation is a hallmark of many autoimmune diseases and modulation of this immune response is therefore of therapeutic interest. Recently the success of B cell therapies in autoimmune diseases has been established. Treatment of rheumatoid arthritis (RA) patients with Rituximab (anti-CD20 therapy) is an accepted clinical therapy by now. More recent clinical trial studies show that treatment with Rituximab also ameliorates disease symptoms in relapsing remitting multiple sclerosis (RRMS) and systemic lupus erythematosus (SLE) patients. This success supports the potential for future therapies in autoimmune diseases targeting B cell immunity.

Bruton's tyrosine kinase (Btk) is a Tec family non-receptor protein kinase, expressed in B cells and myeloid cells. The function of Btk in signaling pathways activated by the engagement of the B cell receptor (BCR) and FcεR1 on mast cells is well established. In addition, a function for Btk as a downstream target in Toll like receptor signaling was suggested. Functional mutations in Btk in humans results in the primary immunodeficiency disease called XLA which is characterized by a defect in B cell development with a block between pro- and pre-B cell stage. This results in an almost complete absence of B lymphocytes in human causing a pronounced reduction of serum immunoglobulin of all classes. These findings support the key role for Btk in the regulation of the production of auto-antibodies in autoimmune diseases. In addition, regulation of Btk may affect BCR-induced production of pro-

inflammatory cytokines and chemokines by B cells, indicating a broad potential for Btk in the treatment of autoimmune diseases.

With the regulatory role reported for Btk in FcεR-mediated mast cell activation, Btk inhibitors may also show potential in the treatment of allergic responses [Gilfillan et al, Immunological Reviews **288** (2009) pp149-169].

Furthermore, Btk is also reported to be implicated in RANKL-induced osteoclast differentiation [Shinohara et al, Cell **132** (2008) pp794-806] and therefore may also be of interest for the treatment of bone resorption disorders.

Other diseases with an important role for dysfunctional B cells are B cell malignancies. Indeed anti-CD20 therapy is used effectively in the clinic for the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia [Lim et al, Haematologica, **95** (2010) pp135-143]. The reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for Btk inhibitors in the treatment of B cell lymphomas as well. Inhibition of Btk seems to be relevant in particular for B cell lymphomas due to chronic active BCR signaling [Davis et al, Nature, **463** (2010) pp 88-92].

Some classes of 6-5 membered fused pyridine ring compounds have been described as kinase inhibitors e.g. Imidazo[1,5-f][1,2,4]triazine compounds have been described in WO2005097800 and WO2007064993. Imidazo[1,5-a]pyrazine compounds have been described in WO2005037836 and WO2001019828 as IGF-1R enzyme inhibitors.

Some of the Btk inhibitors reported are not selective over Src-family kinases. With dramatic adverse effects reported for knockouts of Src-family kinases, especially for double and triple knockouts, this is seen as prohibitive for the development of Btk inhibitors that are not selective over the Src-family kinases.

Both Lyn-deficient and Fyn-deficient mice exhibit autoimmunity mimicking the phenotype of human lupus nephritis. In addition, Fyn-deficient mice also show pronounced neurological defects. Lyn knockout mice also show an allergic-like phenotype, indicating Lyn as a broad negative regulator of the IgE-mediated allergic response by controlling mast cell responsiveness and allergy-associated traits [Odom et al, J. Exp. Med., **199** (2004) pp1491-1502]. Furthermore, aged Lyn knock-out mice develop severe splenomegaly (myeloid expansion) and disseminated monocyte/macrophage tumors [Harder et al, Immunity, **15** (2001) pp603-615]. These observations are in line with hyperresponsive B cells, mast cells and myeloid cells, and increased Ig levels observed in Lyn-deficient mice.

Female Src knockout mice are infertile due to reduced follicle development and ovulation [Roby et al, Endocrine, **26** (2005) pp169-176].

The double knockouts $Src^{-/-}Fyn^{-/-}$ and $Src^{-/-}Yes^{-/-}$ show a severe phenotype with effects on movement and breathing. The triple knockouts $Src^{-/-}Fyn^{-/-}Yes^{-/-}$ die at day 9.5 [Klinghoffer et al, EMBO J., **18** (1999) pp2459-2471]. For the double knockout $Src^{-/-}Hck^{-/-}$, two thirds of the mice die at birth, with surviving mice

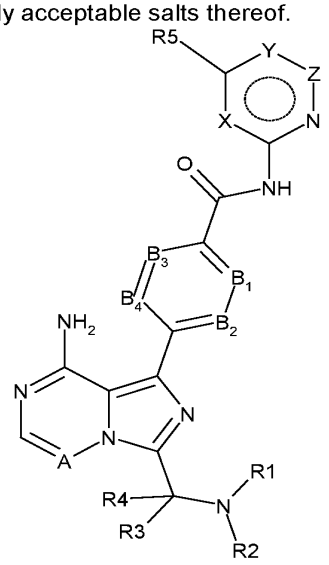
developing osteopetrosis, extramedullary hematopoiesis, anemia, and leukopenia [Lowell et al, Blood, **87** (1996) pp1780-1792].

Hence, an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.

Detailed description of the invention

The object of the present invention is to provide 6-5 membered fused pyridine ring compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

More specifically, the present invention provides 6-5 membered fused pyridine ring compounds according to Formula (I) or pharmaceutically acceptable salts thereof.



Formula (I)

In this formula the substituents are defined as

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or a bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO_2 or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl; all alkyl groups of R5 are optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, halogen or (1-3C)alkoxy;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the carbon atom they are attached to, a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, halogen or (1-3C)alkoxy;

R10 is H, halogen, or (1-3C)alkoxy;

R11 is independently selected from a group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano.

R12 and R13 are independently selected from a group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from a group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl.

With the proviso that:

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y cannot be O or S;
- when Z is CH or N then Y is C(R6) or N and X is CH or N;
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

The terms as used herein refer to the following:

(1-2C)Alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl.

(1-3C)Alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl.

(1-4C)Alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, (1-3C)alkyl groups being preferred.

(1-5C)Alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl and isopentyl, (1-4C)alkyl groups being preferred.

(1-6C)Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. (1-5C)alkyl groups are preferred, (1-4C)alkyl being most preferred.

(1-2C)Alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined.

(1-3C)Alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-2C)alkoxy groups are preferred.

(1-4C)Alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (1-3C)alkoxy groups are preferred, (1-2C)alkoxy groups being most preferred.

(2-4C)Alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl.

(2-6C)Alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and n-pentenyl. (2-4C)alkenyl groups are preferred.

(2-4C)Alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl.

(2-6C)Alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, n-butynyl, n-pentynyl, isopentynyl, isohexynyl or n-hexynyl. (2-4C)alkynyl groups are preferred.

(3-6C)Cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

(3-7C)Cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

(2-6C)Heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom. Preferred heteroatoms are N or O. Preferred are piperidine, morpholine, pyrrolidine and piperazine. Most preferred (2-6C)heterocycloalkyl is pyrrolidine. The heterocycloalkyl group may be attached via a heteroatom if feasible.

(3-7C)Heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O. Preferred (3-7C) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or

morpholinyl. More preferred (3-7C)heterocycloalkyl groups are piperidine, morpholine and pyrrolidine. The heterocycloalkyl group may be attached via a heteroatom if feasible.

(3-7C)Cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom.

(6-10C)Aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl. The preferred (6-10C)aryl group is phenyl.

(1-5C)Heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S. The (1-5C)heteroaryl may optionally be substituted. Preferred (1-5C)heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, more preferred (1-5C)heteroaryl is pyrimidyl.

(1-9C)Heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S. The (1-9C)heteroaryl may optionally be substituted. Preferred (1-9C)heteroaryl groups are quinoline, isoquinoline and indole.

[(1-4C)Alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined. Preferred [(1-4C)alkyl]amino group is methylamino.

Di[(1-4C)alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined. Preferred di[(1-4C)alkyl]amino group is dimethylamino.

Halogen means means fluorine, chlorine, bromine or iodine.

(1-3C)Alkyl-C(O)-S-(1-3C)alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined.

(3-7C)Cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms. Preferred (3-7C)cycloalkenyl groups are cyclopentenyl or cyclohexenyl. Cyclohexenyl groups are most preferred.

(2-6C)Heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S. Preferred (2-6C)heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl groups.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, it is indicated that “all of the alkyl groups” of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (I)indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term “substituted” means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. “Stable compound” or “stable structure” is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term “optionally substituted” means optional substitution with the specified groups, radicals or moieties.

Aspects of the invention

In one aspect the invention relates to a compound according to Formula (I) wherein B1 is C(R7); B2 is C(R8); B3 is C(R9) and B4 is C(R10).

In another aspect the invention relates to a compound according to Formula (I) wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10); R7, R9, and R10 each are H; and R8 is selected from a group consisting of hydrogen and methyl.
In one aspect the invention relates to a compound according to Formula (I) wherein R8 is hydrogen or methyl, in particular R8 is hydrogen.

In another aspect the invention relates to a compound according to Formula (I) wherein R7 is hydrogen, fluorine or (1-3C)alkoxy. In particular, R7 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to Formula (I) wherein R7 is hydrogen.

In yet another aspect the invention relates to a compound according to Formula (I) wherein R9 is hydrogen, fluorine or (1-3C)alkoxy. In particular, R9 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to Formula (I) wherein R9 is hydrogen.

In another aspect the invention relates to a compound according to Formula (I) wherein R10 is hydrogen fluorine or (1-3C)alkoxy. In particular, R10 is hydrogen, fluorine or methoxy. Even more particularly, an aspect of the invention relates to a compound according to Formula (I) wherein R10 is hydrogen.

In still another aspect the invention relates to a compound according to Formula (I) wherein R7 and R8 form, together with the carbon atom they are attached to, an indole or quinoline or naphthyl.
In another aspect the invention relates to a compound according to Formula (I) wherein B1 is C(R7); B2 is C(R8); B3 is C(R9); B4 is C(R10) and R7, R8, R9, and R10 each are H;
In yet another aspect the invention relates to a compound according to Formula (I) wherein R4 is hydrogen or methyl. In particular, R4 is hydrogen.

In still another aspect the invention relates to a compound according to Formula (I) wherein A is N.
In another aspect the invention relates to a compound according ot Formula (I) wherein A is CH.

In another aspect the invention relates to a compound according to Formula (I) wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl, and isoxazolyl. In particular, the invention relates to a compound according to Formula (I) wherein the ring containing X, Y and Z is selected from a group consisting of pyridyl, pyrimidyl and thiazolyl. The definition of R5 and R6 is independent from the selection of X, Y, and Z. The place of attachment of R5 and optionally of R6 to these heteroaryl rings follows from Formula (I).
The invention further relates to a compound according to Formula (I) wherein R5 is selected from a group consisting of hydrogen, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy and (3-6C)cycloalkyl. All of the alkyl groups of R5 are optionally substituted with one or more halogen. In particular, the (1-4C)alkyl group in R5 is optionally substituted with one or more halogen.
In another aspect the invention relates to a compound according to Formula (I) wherein R5 is selected from a group consisting of hydrogen, fluorine, chlorine, (1-3C)alkyl and (1-2C) alkoxy, all of the alkyl groups of R5 are optionally substituted with one or more halogen. In particular, the (1-3C)alkyl group in R5 is optionally substituted with one or more fluoro. Even more particularly, the invention relates to a compound according to Formula (I) wherein R5 is hydrogen, fluorine, methyl, ethyl, propyl, methoxy or trifluoromethyl.

In yet another aspect the invention relates to a compound according to Formula (I) wherein R5 is pyrrolidine or phenyl.

In another aspect, the invention relates to a compound according to Formula (I) wherein R6 is hydrogen or (1-3C)alkyl, preferably R6 is hydrogen.

In yet another aspect the invention relates to a compound according to Formula (I) wherein R5 and R6 together form a (3-7C)cycloalkenyl or a (2-6C)heterocycloalkenyl both optionally substituted with (1-3C)alkyl or one or more halogen. In particular, (3-7C)cycloalkenyl groups are cyclohexenyl and cyclopentenyl. In particular, (2-6C)heterocycloalkenyl groups are azacyclohexenyl and oxycyclohexenyl. Even more in particularly, the invention relates to a compound according to Formula (I) wherein the (3-7C)cycloalkenyl in R5 is cyclohexenyl.

In another aspect, the invention relates to a compound according to Formula (I) wherein R2 is hydrogen or (1-3C)alkyl. In particular, R2 is hydrogen or methyl. R2 is hydrogen being most preferred.

In yet another aspect the invention relates to a compound according to Formula (I) wherein R3 is (1-6C)alkyl. In particular, R3 is (1-3C)alkyl. R3 is methyl being most preferred.
In another aspect the invention relates to a compound according to Formula (I) wherein R3 is (3-7C)cycloalkyl.

In another aspect the invention relates to a compound according to Formula (I) wherein R2 is hydrogen or (1-3C)alkyl and R3 is (1-6C)alkyl. In particular, R2 is hydrogen or methyl and R3 is (1-3C)alkyl. Even more particularly, the invention relates to a compound according to Formula (I) wherein R2 is hydrogen and R3 is methyl.

In yet another aspect the invention relates to a compound according to Formula (I) wherein R2 or R3 are independently selected from a group consisting of cyclopropyl, cyclobutyl and cyclopentyl.

In another aspect the invention relates to a compound of Formula (I) wherein, R2 and R3 form, together with the N and C atom they are attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more halogen, hydroxyl, (1-3C)alkyl. In particular, R2 and R3 form, together with the N and C atom they are attached to, an azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl ring each optionally substituted with one or more halogen, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo, preferred halogen substituent being fluoro.
In yet another aspect the invention relates to a compound of Formula (I) wherein, R2 and R3 form, together with the N and C atom they are attached to, an azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl ring each optionally substituted with fluoro, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo. In particular, R2 and R3, together with the N and C atom they are attached to, form a pyrrolidinyl, piperidinyl, morpholinyl or homopiperidinyl ring.

In yet another aspect the invention relates to a compound according to Formula (I) wherein, R1 is R11C(O) and R11 is (1-6C)alkyl, (2-6C)alkenyl or (2-6C)alkynyl each optionally independently substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (1-3C)alkyl-S-C(O)-(1-3C)alkyl. In particular, the (1-5C)heteroaryl group is pyrimidyl or triazinyl optionally substituted with one or more groups selected from halogen or cyano. In particular, the (3-7C)heterocycloalkyl is pyrrolidinyl. Even more particularly, the invention relates to a compound according to Formula (I) wherein the (3-7C)cycloalkyl substituent of R11 is cyclopropyl. In particular, the (6-10C)aryl substituent of R11 is phenyl.

In yet another aspect the invention relates to a compound according to Formula (I) wherein,
R1 is C(O)R11 and R11 is (2-6C)alkenyl or (2-6C)alkynyl each optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, (di)[(1-

4C)alkyl]amino, (1-3C)alkoxy or (3-7C)cycloalkoxy. In particular, the (3-7C)heterocycloalkyl substituent of R11 is pyrrolidinyl and the (3-7C)cycloalkyl substituent of R11 is cyclopropyl.

In another aspect the invention relates to a compound according to Formula (I) wherein, R1 is C(O)R11 and R11 is (2-4C)alkenyl or (2-4C)alkynyl each optionally substituted with one or more groups selected from (1-4C)alkyl, (3-7C)cycloalkyl, (3-7C)heterocycloalkyl, (di)[(1-4C)alkyl]amino or (1-3C)alkoxy. In particular, the (3-7C)heterocycloalkyl substituent of R11 is pyrrolidinyl and the (3-7C)cycloalkyl substituent is cyclopropyl. Even more particularly, R11 is (2-4C)alkenyl or (2-4C)alkynyl each optionally substituted with one or more groups selected from methyl, ethyl, cyclopropyl, pyrrolidinyl, dimethylamino, methoxy or ethoxy.

In a further aspect the invention relates to compounds according to Formula (I) wherein R1 is C(O)R11 wherein R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano. In particular, the (1-5C)heteroaryl substituent is pyrimidyl or triazinyl, pyrimidyl rings being preferred, optionally substituted with one or more groups selected from halogen or cyano. In particular, the halogen substituent is chlorine.

In another aspect, the invention relates to compounds according to Formula (I) wherein R1 is $R13SO_2$, wherein R13 is (2-6C)alkenyl or (2-6C)alkynyl. In particular, R13 is (2-4C)alkenyl. Even more particularly, R13 is ethenyl.

In another aspect, the invention relates to compounds according to Formula (I) wherein R1 is R12S(O), wherein R12 is (2-6C)alkenyl or (2-6C)alkynyl. In particular, R13 is (2-4C)alkenyl. Even more particularly, R12 is ethenyl.

In yet another aspect, the invention relates to compounds according to Formula (I) wherein R1 is (1-3C)alkyl optionally substituted with R14 wherein R14 is (2-4C)alkenyl or (2-4C)alkynyl.

In yet another aspect the invention relates to a compound according to Formula (I) selected from the group consisting of

(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,
(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,

4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,

4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-S-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate,

(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-methoxypyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,
(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl) imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide,

4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide,

4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide,

(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide,

(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide,
(*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-N-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide,

4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide,
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide,
(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide,
(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide, and
(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide.

The invention also relates to those compounds wherein all specific definitions for R1 through R14 and all substituent groups in the various aspects of the inventions defined here above occur in any combination within the definition of the 6-5 membered fused pyridine ring compounds i.e. 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds of Formula (I).

The 6-5 membered fused pyridine ring compounds like 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds of the invention inhibit the Btk kinase activity. All compounds of the invention have an EC50 of 10 μM or lower.

In another aspect the invention relates to compounds of Formula (I) which have an EC50 of less than 100 nM. In yet another aspect the invention relates to compounds of Formula (I) which have an EC50 of less than 10 nM.

The term EC50 means the concentration of the test compound that is required for 50% inhibition of its maximum effect in vitro.

Inhibition of kinase activity can be measured using the Immobilized Metal Assay for Phosphochemicals (IMAP) assay. IMAP is a homogeneous fluorescence polarization (FP) assay based on affinity capture of phosphorylated peptide substrates. IMAP uses fluorescein-labeled peptide substrates that, upon phosphorylation by a protein kinase, bind to so-called IMAP nanoparticles, which are derivatized with trivalent metal complexes. Binding causes a change in the rate of the molecular motion of the peptide, and results in an increase in the FP value observed for the fluorescein label attached to the substrate peptide (Gaudet et al. A homogeneous fluorescence polarization assay adaptable for a range of protein serine/threonine and tyrosine kinases. J. Biomol. Screen (2003) 8, 164-175).

The compounds of Formula (I) can form salts which are also within the scope of this invention. Reference to a compound of Formula (I) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts. Salts of the compounds of Formula (I) may be formed, for example, by reacting a compound of Formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the

formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

The compounds of Formula (I)may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g. substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may,

for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1975) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (e.g, a drug precursor) that is transformed in vivo to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and V. Stella, “Pro-drugs as Novel Delivery Systems,” Vol. 14 of the A.C.S. Symposium Series, 1975, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of the compounds listed.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The present invention also relates to a pharmaceutical composition comprising 6-5 membered fused pyridine ring compounds like imidazopyrazine and imidazotriazine compounds or pharmaceutically acceptable salts thereof having the general Formula (I) in admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries must be “acceptable” in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The invention further includes a compound of Formula (I) in combination with one or more other drug(s).

Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, intramuscular, nasal, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

In the compounds of generic Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found

in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula (I). For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula (I)can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of 6-5 membered fused pyridine ring compounds or a pharmaceutically acceptable salt thereof, having the general Formula (I) for the manufacture of a medicament to be used for the treatment of Btk-mediated diseases or Btk-mediated conditions.
A further aspect of the invention resides in the use of 6-5 membered fused pyridine ring compounds or a pharmaceutically acceptable salt thereof having the general Formula (I) for the manufacture of a medicament to be used for the treatment of chronic B cell disorders in which T cells play a prominent role.
In yet another aspect the invention resides in the use of 6-5 membered fused pyridine ring compounds like 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine compounds having the general Formula (I) for the manufacture of a medicament to be used for the treatment of Btk-mediated diseases or conditions. These include, but are not limited to, the treatment of B cell lymphomas resulting from chronic active B cell receptor signaling.

Thus, the compounds according to the invention can be used in therapies to treat or prevent diseases Bruton's Tyrosine Kinase (Btk) mediated disorders. Btk mediated disorders or Btk mediated condition as used herein, mean any disease state or other deleterious condition in which B cells, mast cells, myeloid cells or osteoclasts play a central role. These diseases include but are not limited to, immune, autoimmune and inflammatory diseases, allergies, infectious diseases, bone resorption disorders and proliferative diseases.
Immune, autoimmune and inflammatory diseases that can be treated or prevented with the compounds of the present invention include rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis and spondylitis), glomerulonephritis (with or without nephrotic syndrome), autoimmune hematologic disorders (e.g. hemolytic anemia, aplasic anemia, idiopathic thrombocytopenia, and neutropenia), autoimmune gastritis, and autoimmune inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, diabetes (type I and type II), active hepatitis (acute and

chronic), pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis (e.g. Behcet's disease) chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease (e.g. chronic obstructive pulmonary disease) and other inflammatory or obstructive disease on airways.

Allergies that can be treated or prevented include, among others, allergies to foods, food additives, insect poisons, dust mites, pollen, animal materials and contact allergans, type I hypersensitivity allergic asthma, allergic rhinitis, allergic conjunctivitis.

Infectious diseases that can be treated or prevented include, among others, sepsis, septic shock, endotoxic shock, sepsis by Gram-negative bacteria, shigellosis, meningitis, cerebral malaria, pneumonia, tuberculosis, viral myocarditis, viral hepatitis (hepatitis A, hepatitis B and hepatitis C), HIV infection, retinitis caused by cytomegalovirus, influenza, herpes, treatment of infections associated with severe burns, myalgias caused by infections, cachexia secondary to infections, and veterinary viral infections such as lentivirus, caprine arthritic virus, visna-maedi virus, feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Bone resorption disorders that can be treated or prevented include, among others, osteoporosis, osteoarthritis, traumatic arthritis, gouty arthritis and bone disorders related with multiple myeloma.

Proliferative diseases that can be treated or prevented include, among others, non-Hodgkin lymphoma (in particular the subtypes diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)), B cell chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL) with mature B cell, ALL in particular.

In particular compounds of the invention can be used for the treatment of B cell lymphomas resulting from chronic active B cell receptor signaling.

Inhibition of kinase activity can be measured using the Immobilized Metal Assay for Phosphochemicals (IMAP) assay. IMAP is a homogeneous fluorescence polarization (FP) assay based on affinity capture of phosphorylated peptide substrates. IMAP uses fluorescein-labeled peptide substrates that, upon phosphorylation by a protein kinase, bind to so-called IMAP nanoparticles, which are derivatized with trivalent metal complexes. Binding causes a change in the rate of the molecular motion of the peptide, and results in an increase in the FP value observed for the fluorescein label attached to the substrate peptide.

The Btk activity can also be determined in B cell lines such as Ramos cells or in primary cell assays, e.g PBMC or whole blood from human, monkey, rat or mouse or isolated splenocytes from monkey, rat or mouse. Inhibition of Btk activity can be investigated measuring anti-IgM-induced MIP1β production

(Ramos, PBMC, splenocytes), H_2O_2-induced Btk and PLCγ2 phosphorylation (Ramos cells), or anti-IgM-induced B cell proliferation or CD86 expression on primary B cells (PBMC and splenocytes).

Regulation of Btk activity can also be determined on human, monkey, rat or mouse mast cells following activation FcεR induced degranulation, cytokine production and CD63 induced cell surface expression.

Furthermore, regulation of Btk activity can be determined on CD14+ monocytes differentiated following treatment with M-CSF to osteoclasts and activated with RANKL.

Activity of Btk inhibitors can be investigated in mouse splenocytes following administration *in vivo*. In a typical experiment mice can be euthanized 3h following compound administration. Spleens can be extracted from the treated mice for splenocyte isolation. Splenocytes can be plated in 96 well culture plates and stimulated with anti-IgM, without further addition of compounds. Anti-IgM-induced B cell stimulation and inhibition thereof by Btk inhibitors can be measured by B cell proliferation, MIP1β production or CD86 expression on CD19+ splenocyte B cells.

Efficacy of Btk inhibitors can also be investigated in the mouse collagen induced arthritis model using a therapeutic protocol with start of treatment following onset of disease, measuring disease score, X-ray analysis of bone destruction, cartilage breakdown and histology of joints

Efficacy of Btk inhibitors on the regulation of activated mast cells can be investigated in vivo using the passive cutaneous anaphylaxis model.

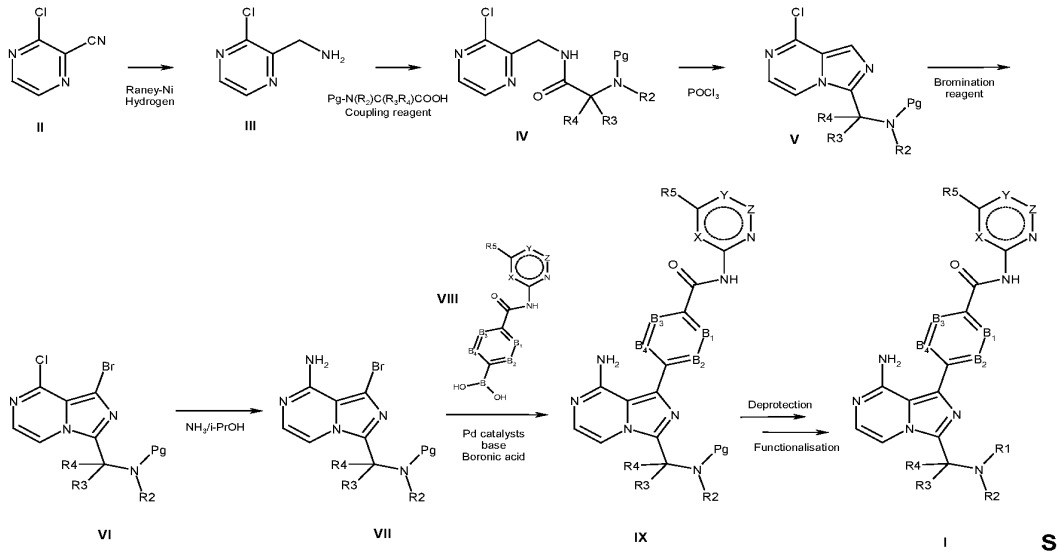
The effect of Btk inhibitors on bone resorption in vivo can be investigated using the rat OVX model. In this model ovariectomized animals develop symptoms of osteoporosis that may be regulated using a Btk inhibitor.

General Synthesis

The 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention can be prepared by methods well known in the art of organic chemistry. See, for example, J. March, '*Advanced Organic Chemistry*' 4th Edition, John Wiley and Sons. During synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This is achieved by means of conventional protecting groups, such as those described in T.W. Greene and P.G.M. Wutts '*Protective Groups in Organic Synthesis*' 3rd Edition, John Wiley and Sons, 1999. The protective groups are optionally removed at a convenient subsequent stage using methods well known in the art.

The products of the reactions are optionally isolated and purified, if desired, using conventional techniques, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials are optionally characterized using conventional means, including physical constants and spectral data.

8-amino-imidazo[1,5-a]pyrazine compounds of Formula (I), wherein R_1-R_5 have the previously defined meanings, can be prepared by the general synthetic route shown in scheme I



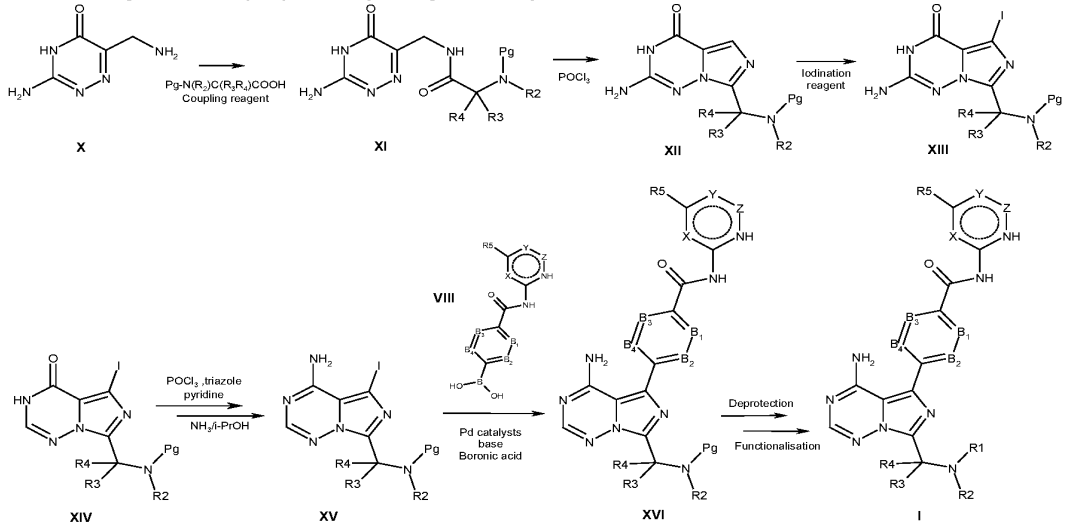
Scheme I

Reduction of 3-chloropyrazine-2-carbonitrile (**II**) can be accomplished by hydrogenation in the presence of a suitable catalysts system and solvent, for example Raney-Nickel to provide (3-chloropyrazin-2-yl)methanamine (**III**). This can then be reacted with an appropriately amine protected amino acid. The reaction of Cbz-N(R_2)CR_3R_4)COOH can be carried out in a solvent such as DMF, THF or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, 4-DMAP or triethylamine and in the presence of a coupling reagent such as PyBOP, TBTU, EDCI or HATU to form N-((3-chloropyrazin-2-yl)methyl)amide **IV**. Cyclisation of chloropyrazine **IV** can be performed using condensation reagents like phosphorous oxychloride under heating conditions to provide the 8-chloroimidazo[1,5-a]pyrazine derivatives **V**. Subsequent bromination can be accomplished using bromine or N-bromosuccinimide in a suitable solvent like DCM or DMF at appropriate temperature to obtain compounds of formula **VI**. 8-Aminoimidazo[1,5-a]pyrazine derivatives (**VII**) can be prepared from compounds **VI** using ammonia(gas) in isopropanol at elevated temperature in a pressure vessel (>4 atm). Compounds of formula **IX** can be prepared from compounds of formula **VII** using an appropriate boronic acid or pinacol ester (**VIII**), in the presence of a suitable palladium catalyst system and solvent, for example bis(diphenylphosphino)ferrocene palladium(II)chloride complex or *tetrakis*(triphenylphosphine)palladium(0) in the presence of potassium carbonate in dioxane/water provide compounds of formula **IX**. Finally, cleaving the protective group of compounds with the formula **IX** give the unprotected amine which after functionalisation, using methods well known in the art, with appropriate warheads with previously defined meanings, provided compounds of Formula (I). An example of such protective strategy is the use of the benzyloxycarbonyl protecting group to protect the amine from the amino acids used, and after deprotection with 33% HBr/HOAc or conc. HCl gave the resulting amines.

The amino acids HN(R_2)CR_3R_4)COOH are either commercially available or they can be readily prepared using methods well known to the skilled organic chemist, to introduce protecting groups like benzyloxycarbonyl or *tert*-butyloxycarbonyl.

Palladium catalysts and conditions to form either the pinacol esters or to couple the boronic acids or pinacol esters with the 1-bromoimidazo[1,5-a]pyrazin-8-amine are well known to the skilled organic chemist – see, for example, Ei-ichi Negishi (Editor), Armin de Meijere (Associate Editor), Handbook of Organopalladium Chemistry for Organic Synthesis, John Wiley and Sons, 2002.

4-Amino-imidazo[1,5-f][1,2,4]triazine compounds of Formula (I), wherein R_1-R_5 have the previously defined meanings, can be prepared by the general synthetic route shown in scheme II



Scheme II

Starting material 3-amino-6-(aminomethyl)-1,2,4-triazin-5(4H)-one **X** can be prepared via a condensation reaction of ethyl bromopyruvate, dibenzylamine, and aminoguanidine carbonate, followed by debenzylation via hydrogenation over Pd-C catalyst [Mitchel, W.L.et al, *J. Heterocycl. Chem.* **21** (1984) pp697].This can then be reacted with an appropriately amine protected amino acid. The reaction of Cbz-$N(R_2)CR_3R_4)COOH$ can be carried out in a solvent such as DMF, THF or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, 4-DMAP or triethylamine and in the presence of a coupling reagent such as PyBOP, TBTU, EDCI or HATU to form N-((3-amino-5-oxo-4,5-dihydro-1,2,4-triazin-6-yl)methyl)amide **XI**. Cyclisation of the amino-triazinone **XI** can be performed using condensation reagents like phosphorous oxychloride under heating conditions to provide the 2-aminoimidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XII**. Subsequent iodination can be accomplished using iodine or N-iodosuccinimide in a suitable solvent like DCM or DMF at appropriate temperature to obtain compounds of formula **XIII**. Removal of the 2-amino group in the 2-aminoimidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XIII** can be perfomed using t-butyl nitrite in solvents like DMF/THF at room temperature to form imidazo[1,5-f][1,2,4]triazin-4(3H)-one derivatives **XIV**. 4-Amino-imidazo[1,5-f][1,2,4]triazine derivatives (**XV**) can be prepared from compounds **XIV** using phosphorousoxychloride, 1,2,4-triazole in pyridine and subsequent ammonolysis with ammonia(gas) in isopropanol at room temperature. Compounds of formula **XVI** can be prepared from compounds of formula **XV** using an appropriate boronic acid or pinacol ester (**VIII**), in the presence of a suitable palladium catalyst system and solvent, for example bis(diphenylphosphino)ferrocene palladium(II)chloride complex or

tetrakis(triphenylphosphine)palladium(0) in the presence of potassium carbonate in dioxane/water provide compounds of formula **XVI**. Finally, cleaving the protective group of compounds with the formula **XVI** give the unprotected amine which after functionalisation, using methods well known in the art, with appropriate warheads with previously defined meanings, provided compounds of Formula (I). An example of such protective strategy is the use of the benzyloxycarbonyl protecting group to protect the amine from the amino acids used, and after deprotection with 33% HBr/HOAc or conc. HCl gave the resulting amines.

The amino acids $HN(R_2)CR_3R_4)COOH$ are either commercially available or they can be readily prepared using methods well known to the skilled organic chemist, to introduce protecting groups like benzyloxycarbonyl or *tert*-butyloxycarbonyl.

Palladium catalysts and conditions to form either the pinacol esters or to couple the boronic acids or pinacol esters with the 5-iodoimidazo[1,5-f][1,2,4]triazin-4-amine are well known to the skilled organic chemist – see, for example, Ei-ichi Negishi (Editor), Armin de Meijere (Associate Editor), Handbook of Organopalladium Chemistry for Organic Synthesis, John Wiley and Sons, 2002.

The present invention also includes within its scope all stereoisomeric forms of the 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives according to the present invention resulting, for example, because of configurational or geometrical isomerism. Such stereoisomeric forms are enantiomers, diastereoisomers, *cis* and *trans* isomers *etc.* For example where azepane-2-carboxylic acid is used as amino acid, there exists a mixture of two enantiomers. In the case of the individual stereoisomers of compounds of Formula (I) or salts or solvates thereof, the present invention includes the aforementioned stereoisomers substantially free, *i.e.*, associated with less than 5%, preferably less than 2% and in particular less than 1% of the other stereoisomer. Mixtures of stereoisomers in any proportion, for example a racemic mixture comprising substantially equal amounts of two enantiomers are also included within the scope of the present invention.

For chiral compounds, methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, *e.g.* synthesis with chiral induction, synthesis starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers using chromatography on chiral media. Such methods are described in *Chirality In Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Likewise methods for synthesis of geometrical isomers are also well known in the art.

The 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salts may also be obtained by treating the free base of Formula (I) with an organic or inorganic acid such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, malonic acid, methanesulphonic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, and ascorbic acid.

The 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention also exist as amorphous forms. Multiple crystalline forms are also possible. All the physical forms are included within the scope of the present invention.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of Formula (I)(e.g. those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically-labeled compounds of Formula (I)can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labeled reagent for a non-isotoplically labeled reagent.

The invention is illustrated by the following examples.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

Mass Spectrometry: Electron Spray spectra were recorded on the Applied Biosystems API-165 single quad mass spectrometer in alternating positive and negative ion mode using Flow Injection. The mass range was 120-2000 Da and scanned with a step rate of 0.2 Da. and the capillary voltage was set to 5000 V. N2-gas was used for nebulisation.

LC-MS spectrometer (Waters) Detector: PDA (200-320 nm), Mass detector: ZQ

Eluent: A: acetonitrile with 0.05% trifluoroacetic acid, B: acetronitrile / water = 1/9 (v/v) with 0.05% trifluoroacetic acid

Method LCMS (A)

Column 1: Chromolith Performance, RP-18e, 4.6x100 mm,

Gradient method: Flow: 4 mL/min

Time (min)	A (%)	B (%)
0.00	100	0
3.60	0	100
4.00	0	100
4.05	100	0
6.00	100	0

Method LCMS (B)

Column 2: XBridge C18, 3.5µm, 4.6x20mm

Gradient method: Flow: 4 ml/min

Time (min.)	A (%)	B (%)
0.0	100	0
1.60	0	100
3.10	0	100
3.20	100	0
5.00	100	0

UPLC : Water acquity UPLC system; Column : BEH C18 1.7 µm, 2.1 x 100 mm, Detector: PDA (200-320 nm), Mass detector: SQD

Eluent: A: acetonitrile with 0.035% trifluoroacetic acid, B: acetronitrile / water = 1/9 (v/v) with 0.035% trifluoroacetic acid

Method	**UPLC (A)**		**UPLC (B)**		**UPLC (C)**	
	Method 60_100		*Method 40_80*		*Method 0_60*	
	Flow: 0.75 mL/min		Flow: 0.65 mL/min		Flow: 0.60 mL/min	
Time (min)	A (%)	B (%)	A (%)	B (%)	A (%)	B (%)
0.0	40	60	60	40	100	0
3.00	0	100	20	80	40	60
3.20	0	100	0	100	0	100
3.69	0	100	0	100	0	100
3.70	40	60	60	40	100	0

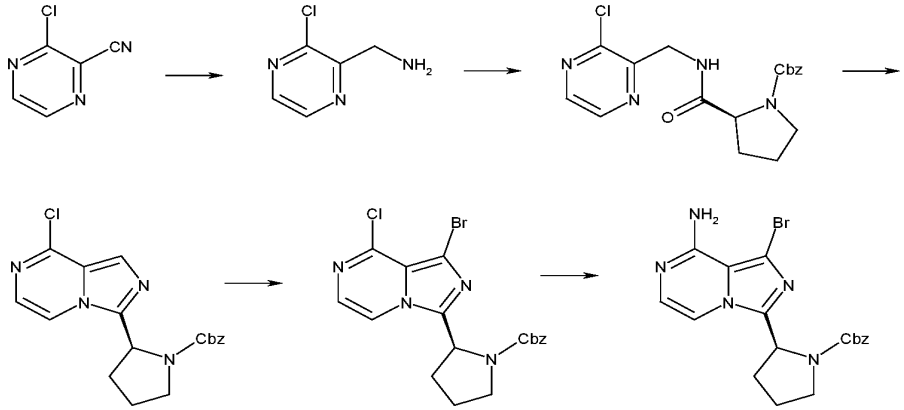
Preparative HPLC was conducted on a column (50 x 10 mm ID, 5µm, Xterra Prep MS C18) at a flow rate of 5 ml/min, injection volume 500 µl, at room temperature and UV Detection at 210 nm.

The following abbreviations are used throughout the application with respect to chemical terminology:

HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate
Cbz	Benzyloxycarbonyl
DMF	N,N-Dimethylformamide
DCM	Dichloromethane
EtOAc	Ethyl acetate
DIPEA	N,N-Diisopropylethylamine
THF	Tetrahydrofuran
EtOH	Ethanol
EDCI.HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide. hydrochloride
4-DMAP	4-Dimethylamino pyridine
PyBOP	O-Benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate
TBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
HBr	Hydrogen bromide
HCl	Hydrogen chloride
HOAc	Acetic acid
Z	Benzyloxycarbonyl
Pro	Proline
$POCl_3$	Phosphorous oxychloride
HPLC	High Pressure Liquid Chromatography
UPLC	Ultra Performance Liquid Chromatography
LiHMDS	Lithium hexamethyldisilazide
MeOH	Methanol
Gly	Glycine
Ala	Alanine
n-BuLi	n-Butyllithium
CO_2	Carbon dioxide

The names of the final products in the examples are generated using Chemdraw Ultra (version 9.0.7).

Intermediate 1



(*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(a) (3-Chloropyrazin-2-yl)methanamine.hydrochloride

To a solution of 3-chloropyrazine-2-carbonitrile (160 g, 1.147 mol) in acetic acid (1.5 L) was added Raney Nickel (50% slurry in water, 70 g, 409 mmol). The resulting mixture was stirred under 4 bar hydrogen at room temperature overnight. Raney Nickel was removed by filtration over decalite and the filtrate was concentrated under reduced pressure and co-evaporated with toluene. The remaining brown solid was dissolved in ethyl acetate at 50°C and cooled on an ice-bath. 2M hydrogen chloride solution in diethyl ether (1.14 L) was added in 30 min. The mixture was allowed to stir at room temperature over weekend. The crystals were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C. The product brown solid obtained was dissolved in methanol at 60°C. The mixture was filtered and partially concentrated, cooled to room temperature and diethyl ether (1000 ml) was added. The mixture was allowed to stir at room temperature overnight. The solids formed were collected by filtration, washed with diethyl ether and dried under reduced pressure at 40°C to give 153.5 g of (3-chloropyrazin-2-yl)methanamine.hydrochloride as a brown solid (74.4 %, content 77 %).

(b) (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate

To a solution of (3-chloropyrazin-2-yl)methanamine.HCl (9.57 g, 21.26 mmol, 40% wt) and Z-Pro-OH (5.3 g, 21.26 mmol) in dichloromethane (250 mL) was added triethylamine (11.85 mL, 85 mmol) and the reaction mixture was cooled to 0°C. After 15 min stirring at 0°C, HATU (8.49 g, 22.33 mmol) was added. The mixture was stirred for 1 hour at 0°C and then overnight at room temperature. The mixture was washed with 0.1 M HCl-solution, 5% $NaHCO_3$, water and brine, dried over sodium sulfate and concentrated *in vacuo*. The product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 5 g of (*S*)-benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (62.7%).

(c) (*S*)-Benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(*S*)-Benzyl 2-((3-chloropyrazin-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (20.94 mmol, 7.85 g) was dissolved in acetonitrile (75 ml), 1,3-dimethyl-2-imidazolidinone (62.8 mmol, 6.9 ml, 7.17 g) was added and the reaction mixture was cooled to 0ºC before $POCl_3$ (84 mmol, 7.81 ml, 12.84 g) was added drop

wise while the temperature remained around 5ºC. The reaction mixture was refluxed at 60-65°C overnight. The reaction mixture was poured carefully in ammonium hydroxide 25% in water (250 ml)/crushed ice (500 ml) to give a yellow suspension (pH ~8-9) which was stirred for 15 min until no ice was present in the suspension. Ethyl acetate was added, layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered and evaporated to give 7.5 g crude product. The crude product was purified using silica gel chromatography (heptane/ethyl acetate = 1/4 v/v%) to give 6.6 g of (*S*)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (88%).

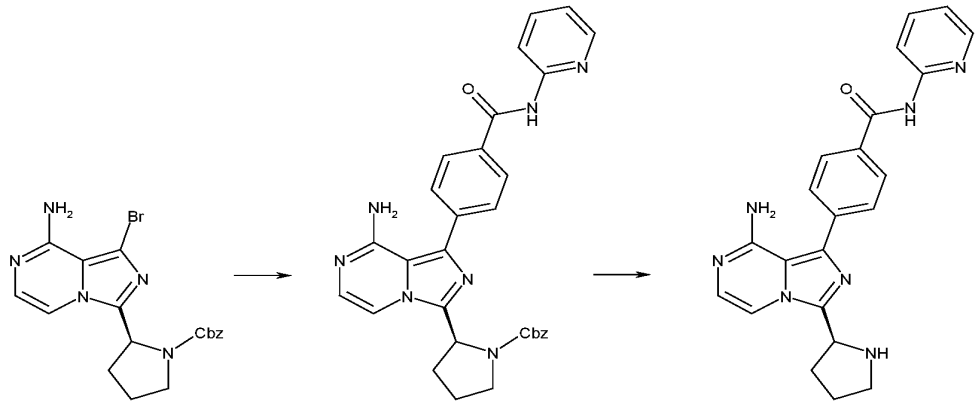
(d) (*S*)-Benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

N-Bromosuccinimide (24.69 mmol, 4.4 g) was added to a stirred solution of (*S*)-benzyl 2-(8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (24.94 mmol, 8.9 g) in DMF (145 mL). The reaction was stirred 3 h at rt. The mixture was poured (slowly) in a stirred mixture of water (145 mL), ethyl acetate (145 mL) and brine (145 mL). The mixture was then transferred into a separating funnel and extracted. The water layer was extracted with 2x145 mL ethyl acetate. The combined organic layers were washed with 3x300 mL water, 300 mL brine, dried over sodium sulfate, filtered and evaporated. The product was purified using silica gel chromatography (ethyl acetate/heptane = 3/1 v/v%) to give 8.95 g of (S)-benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (82.3%).

(e) (*S*)-Benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(*S*)-Benzyl 2-(1-bromo-8-chloroimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (20.54 mmol, 8.95 g) was suspended in 2-propanol (113 ml) in a pressure vessel. 2-propanol (50 ml) was cooled to -78ºC in a pre-weighed flask (with stopper and stirring bar) and ammonia gas (646 mmol, 11 g) was led through for 15 minutes. The resulting solution was added to the suspension in the pressure vessel. The vessel was closed and stirred at room temperature and a slight increase in pressure was observed. Then the suspension was heated to 110 °C which resulted in an increased pressure to 4.5 bar. The clear solution was stirred at 110 ºC, 4.5 bar overnight. After 18h the pressure remained 4 bar. The reaction mixture was concentrated in vacuum, the residue was suspended in ethyl acetate and subsequently washed with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, saturated sodium chloride solution, dried over sodium sulfate and concentrated to give 7.35 g of (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (86%).

Intermediate 2



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

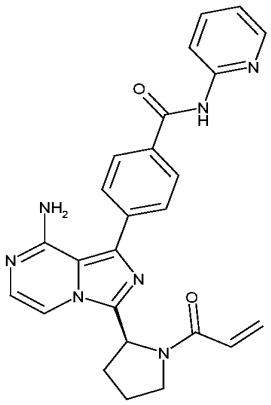
(a) (*S*)-Benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate

(S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.237 mmol, 98.5 mg) and 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid (0.260 mmol, 63.0 mg) were suspended in a mixture of 2N aqueous potassium carbonate solution (2.37 mmol, 1.18 mL) and dioxane (2.96 mL). Nitrogen was bubbled through the mixture, followed by the addition of 1,1'-bis(diphenylphosphino)ferrocene palladium (ii) chloride (0.059 mmol, 47.8 mg). The reaction mixture was heated for 20 minutes at 140°C in the microwave. Water was added to the reaction mixture, followed by an extraction with ethyl acetate (2x). The combined organic layer was washed with brine, dried over magnesium sulfate and evaporated. The product was purified using silica gel and dichloromethane/methanol = 9/1 v/v% as eluent to afford 97.1 mg of (*S*)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (77%).

(b) (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To (S)-benzyl 2-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (0.146 mmol, 78 mg) was added a 33% hydrobromic acid/acetic acid solution (11.26 mmol, 2 ml) and the mixture was left at room temperature for 1 hour. The mixture was diluted with water and extracted with dichloromethane. The aqueous phase was neutralized using 2N sodium hydroxide solution, and then extracted with dichloromethane. the organic layer was dried over magnesium sulfate, filtered and evaporated to give 34 mg of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (58%).

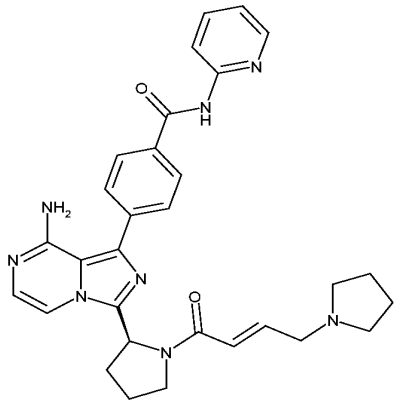
Example 1



(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a solution of (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (0.626 mmol, 250 mg) in dichloromethane (25 ml) at 0 °C was added triethylamine (0.626 mmol, 0.087 ml, 63.3 mg) and, drop wise, acryloyl chloride (0.657 mmol, 0.053 ml, 59.5 mg). The resulting mixture was stirred at 0 °C for 2 hours. The mixture was washed with water, dried over magnesium sulfate. After evaporation, the residue was purified by preparative HPLC. Fractions containing product were collected and lyophilized to afford 126 mg of (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (44.4% yield). Data: UPLC (C) R_t : 1.50 min; *m/z* 454.3 $(M+H)^+$.

Example 2

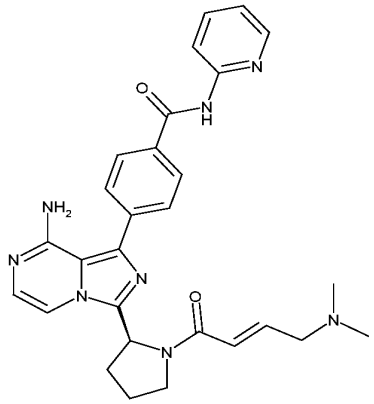


(*S*,*E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a solution of (*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 2b, 19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) and (*E*)-4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride (9.45 mg, 0.049 mmol) in dichloromethane (2 mL) was added HATU (18.75 mg, 0.049 mmol). The mixture was stirred for 30 min at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated *in vacuo*. The residue

was purified by preparative HPLC. Fractions containing product were collected and reduced to dryness to afford 7.1 mg of (*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (26.8 % yield). Data: UPLC (C) R_t : 1.25 min; *m/z* 537.4 $(M+H)^+$.

Example 3



(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

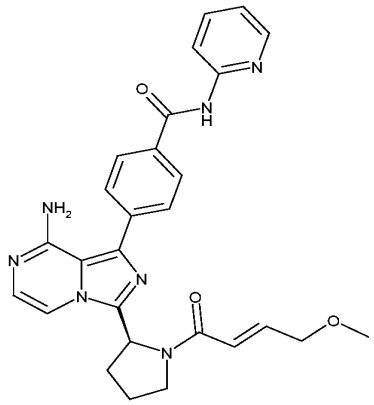
This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (11.8 mg, 46.6%). Data: UPLC (C) R_t : 1.29 min; *m/z* 511.0 $(M+H)^+$.

Intermediate 3

(*E*)-4-Methoxybut-2-enoic acid

Sodium methoxide (30%/Methanol, 30.3 mmol, 5.68 mL) was added via a glass syringe to a stirred solution of 4-bromocrotonic acid (6.06 mmol, 1 g) in methanol (60 mL) at room temperature. The light yellow solution was stirred for 30 min at room temperature and 2 h. at reflux. After cooling the reaction mixture, the solvent was removed under reduced pressure. The residue was partitioned between water (50 mL) and diethyl ether (50 mL). 2M aq. hydrochloride solution (3.5 mL) was added until pH was ~pH 1. The water layer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*, to give 650 mg of (*E*)-4-Methoxybut-2-enoic acid (92%).

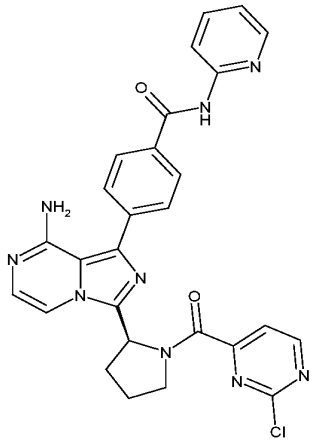
Example 4



(*S*,*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (11 mg, 29.9%). Data: UPLC (C) R_t : 1.58 min; *m/z* 498.3 $(M+H)^+$.

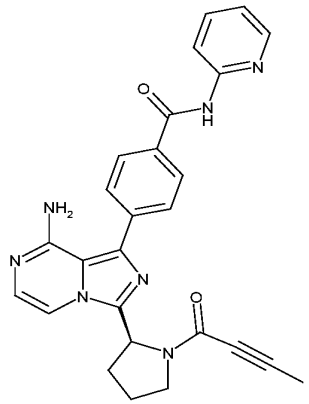
Example 5



(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 2-chloropyrimidine-4-carboxylic acid, to afford the title compound (8.3 mg, 40.4%). Data: UPLC (C) R_t : 1.64 min; *m/z* 540.1 $(M+H)^+$.

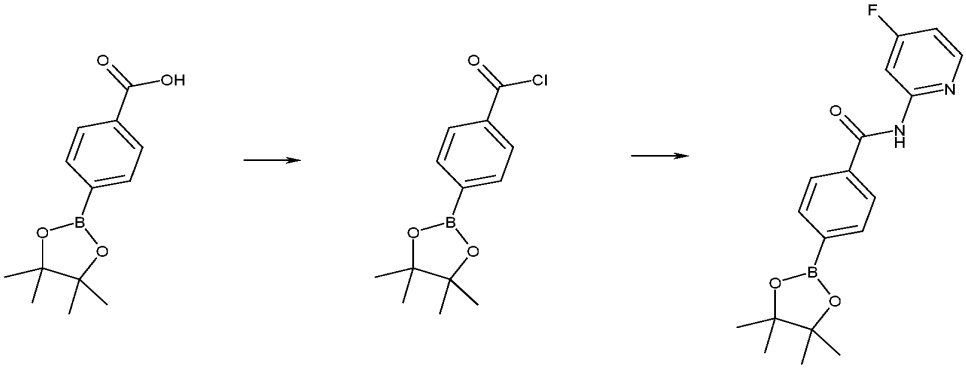
Example 6



(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 2-butynoic acid, to afford the title compound (10.5 mg, 18.0%). Data: LCMS (B) R_t : 2.08 min; *m/z* 466.1 $(M+H)^+$.

Intermediate 4



N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

(a) 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride

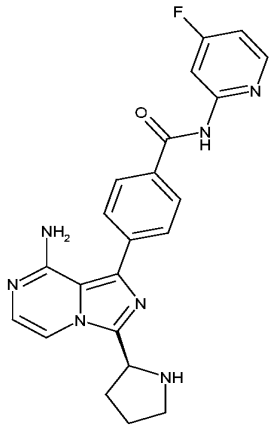
To a cold (0°C) solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (40.3 mmol, 10.01 g) in dichloromethane (206 mL) was added a catalytic amount of DMF. A solution of oxalyl chloride (101 mmol, 8.66 mL, 12.8 g) was added drop wise. After stirring for 30 min at 0°C, the reaction mixture was allowed to warm up to room temperature and the mixture was stirred for an additional 3 hours. The reaction mixture was concentrated to give 10.9 g. of crude 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (101%).

(b) N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (1.688 mmol, 450 mg) in acetonitrile (24.8 mL) was added 2-amino-4-fluoropyridine (4.22 mmol, 473 mg). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated to a small volume, 3% aq. citric acid solution (18 mL) was added and the mixture was extracted with dichloromethane (2 x 15

mL). The combined organic layer was washed with 3% aq. citric acid solution, dried over magnesium sulfate, filtered and evaporated to afford 542.2 mg of N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (94%) as an off-white solid.

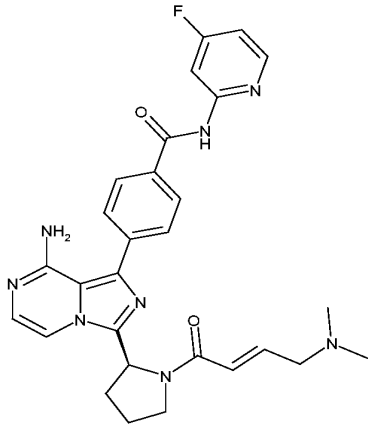
Intermediate 5



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2b, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 4b) to afford the title compound (331 mg, 93%).

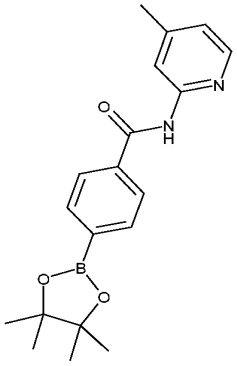
Example 7



(*S,E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 5 and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (33.4 mg, 54.1%). Data: UPLC (C) R_t : 1.72 min; *m/z* 529.3 $(M+H)^+$.

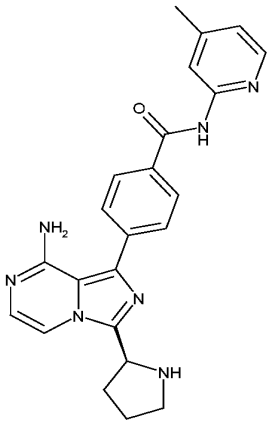
Intermediate 6



N-(4-Methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

To a stirred solution of 4-methylpyridin-2-amine (7.86 mmol, 850 mg) in THF (50 mL) was added dropwise a solution of 1M LiHMDS in THF (8.0 mmol, 8 mL) at room temperature. After the reaction mixture turned dark green, a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl chloride (9.6 mmol, 2.56 g) in dichloromethane (55 mL) was added dropwise. The mixture was stirred at room temperature for 2.5 h and was then concentrated. 3% aq. Citric acid solution (18 mL) was added and the mixture was extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with 3% aq. citric acid solution, dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in THF (15 mL) and 6M NaOH solution (15 mL) was added. The mixture was stirred for 4 h. at room temperature. Ethyl acetate was added and the layers were separated. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica (eluent: DCM/MeOH=98/2 to DCM/MeOH=95/5) to yield 1.1 g of N-(4-methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (40.7%).

Intermediate 7

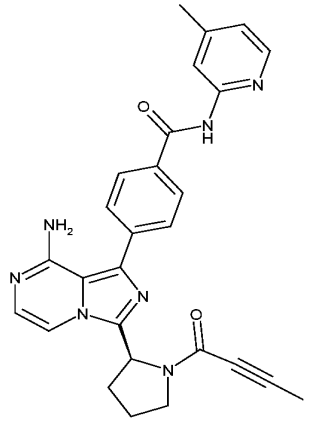


(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-

methylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 6) to afford the title compound (125.5 mg, 82%).

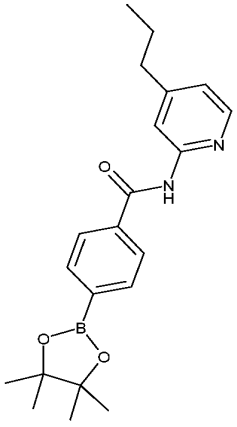
Example 8



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide (intermediate 7) and 2-butynoic acid, to afford the title compound (6.3 mg, 27.2%). Data: UPLC (C) R_t : 1.56 min; *m/z* 480.3 $(M+H)^+$.

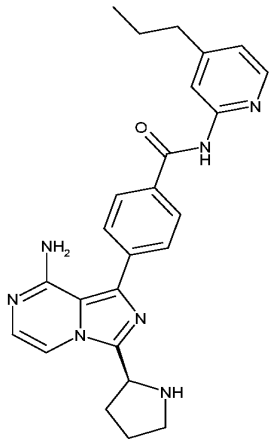
Intermediate 8



N-(4-Propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 6, starting from 4-propylpyridin-2-amine, to afford the title compound (371.5 mg, 54.1%).

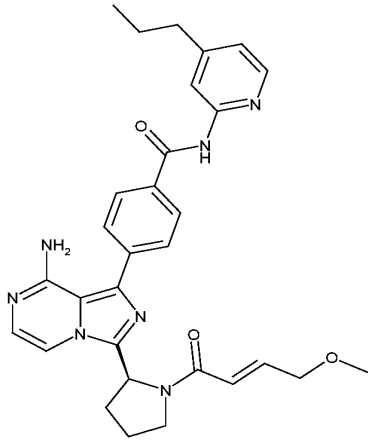
Intermediate 9



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-Propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 8) to afford the title compound (147.8 mg, 93%).

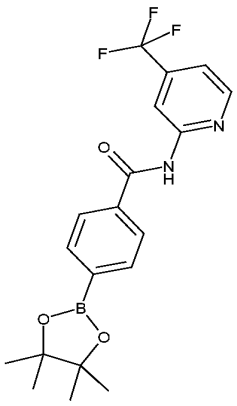
Example 9



(*S*,*E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide (intermediate 9) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (30.9 mg, 65.7%). Data: UPLC (C) R_t : 2.73 min; *m/z* 566.3 $(M+H)^+$.

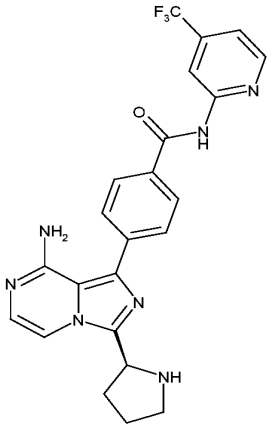
Intermediate 10



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 6, starting from 4-(trifluoromethyl)pyridin-2-amine, to afford the title compound (657.2 mg, 89%).

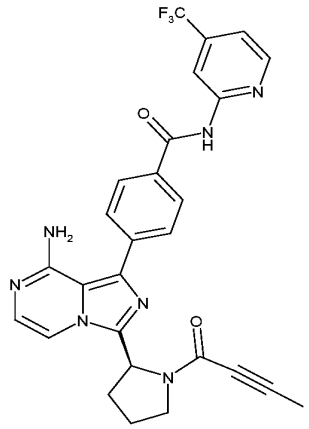
Intermediate 11



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 10) to afford the title compound (163 mg, 87%).

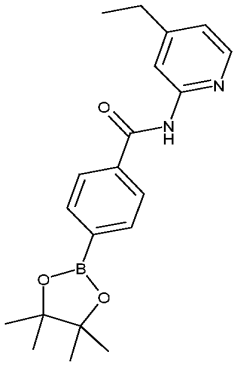
Example 10



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 11) and 2-butynoic acid, to afford the title compound (7.1 mg, 31.1%). Data: UPLC (C) R_t : 2.63 min; *m/z* 534.2 $(M+H)^+$.

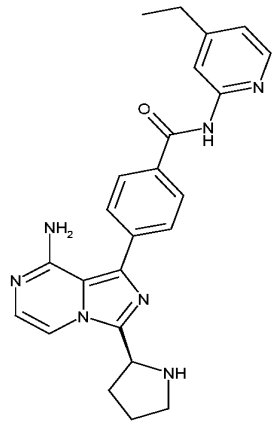
Intermediate 12



N-(4-Ethylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 4, starting from 4-ethylpyridin-2-amine, to afford the title compound (334.5 mg, 50.6%).

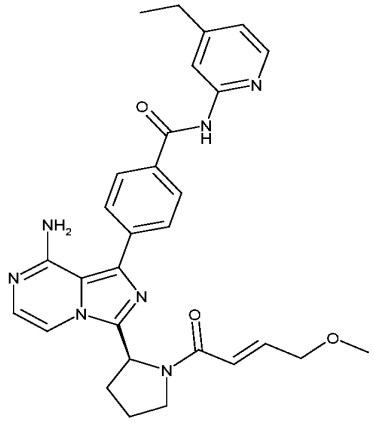
Intermediate 13



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4-ethylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 12) to afford the title compound (133.8 mg, 89%).

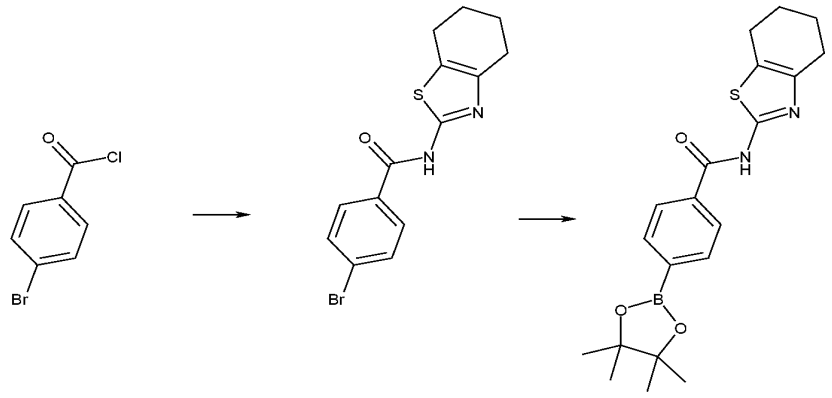
Example 11



(*S*,*E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide (intermediate 13) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (10.6 mg, 28.8%). Data: UPLC (C) R_t : 1.60 min; *m/z* 526.3 $(M+H)^+$.

Intermediate 14



N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

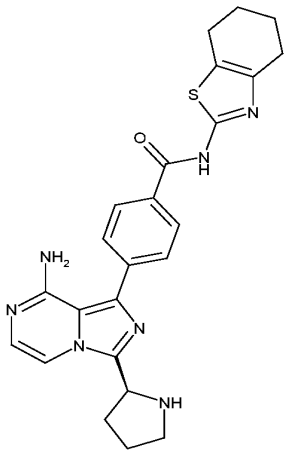
(a) 4-Bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

4-Bromobenzoyl chloride (1.5 g, 6.83 mmol) and 4,5,6,7-Tetrahydro-1,3-benzothiazol-2-amine (1.054 g, 6.83 mmol) were dissolved in Pyridine (15 ml) and stirred at 50°C for 1.5 h. The reaction mixture was cooled to room temperature and poured in water. The solid formed was filtered, washed with water. The solids were co-evaporated with toluene twice to afford 1.8 g of 4-bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (78%) as a yellow solid.

(b) N-(4,5,6,7-Tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)benzamide

To a solution of 4-bromo-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (1.8 g, 5.34 mmol) dioxane (40 ml) was added bis(pinacolato)diboron (1.762 g, 6.94 mmol) and potassium acetate (1.048 g, 10.68 mmol). The reaction mixture was degassed with nitrogen. Subsequently 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride (0.218 g, 0.267 mmol) was added and the reaction mixture was stirred at 80°C for 5 days. The mixture was cooled to room temperature and after addition of water extracted three times with EtOAC. The organic layers were combined, washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified using silica gel chromatography (heptane/ethyl acetate 3/7 to 7/3 v/v%) to give 600 mg of N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)benzamide (29.3%).

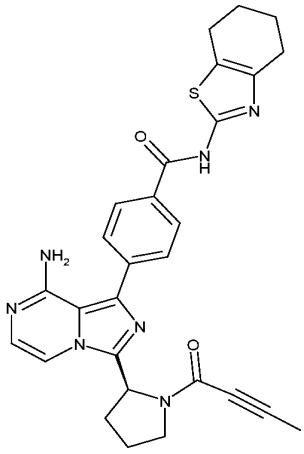
Intermediate 15



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 14b) to afford the title compound (260 mg, 60%).

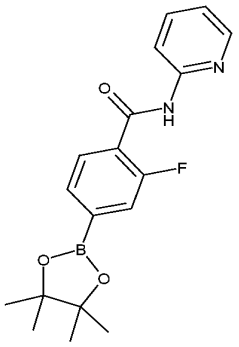
Example 12



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (S)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide (intermediate 15) and 2-butynoic acid, to afford the title compound (7 mg, 19.2%). Data: UPLC (C) R_t : 2.41 min; *m/z* 526.3 $(M+H)^+$.

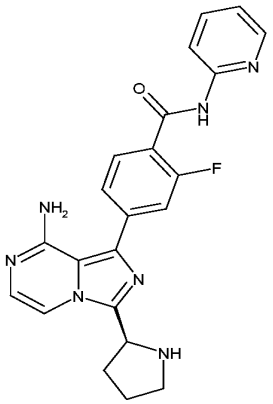
Intermediate 16



2-Fluoro-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 4-bromo-2-fluorobenzoic acid, to afford the title compound (2.54 g, 76%).

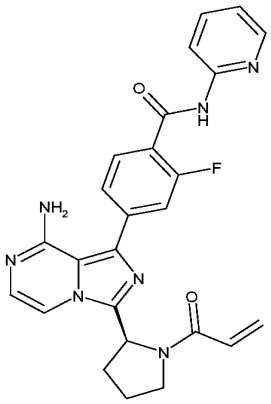
Intermediate 17



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 2-Fluoro-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 16) to afford the title compound (160 mg, 76%).

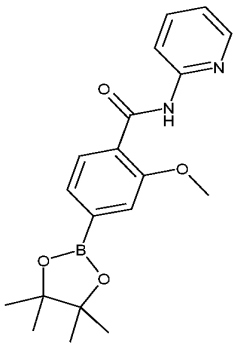
Example 13



(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide (intermediate 17) and acryloylchloride, to afford the title compound (13 mg, 38.4%). Data: UPLC (C) R_t : 1.67 min; *m/z* 472.3 $(M+H)^+$.

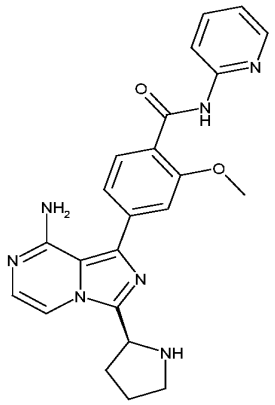
Intermediate 18



2-Methoxy-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 4-bromo-2-methoxybenzoic acid, to afford the title compound (2.6 g, 90%).

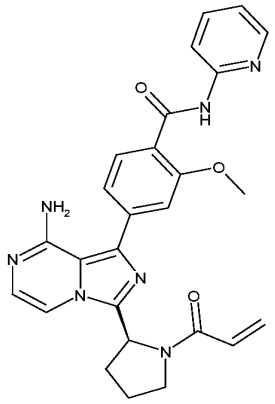
Intermediate 19



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and 2-methoxy-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (intermediate 18) to afford the title compound (175 mg, 56.6%).

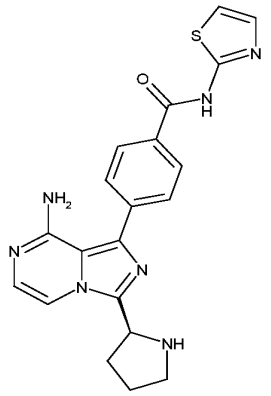
Example 14



(*S*)-4-(3-(1-Acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide (intermediate 19) and acryloylchloride, to afford the title compound (14 mg, 35.5%). Data: UPLC (C) R_t : 1.74 min; *m/z* 484.3 $(M+H)^+$.

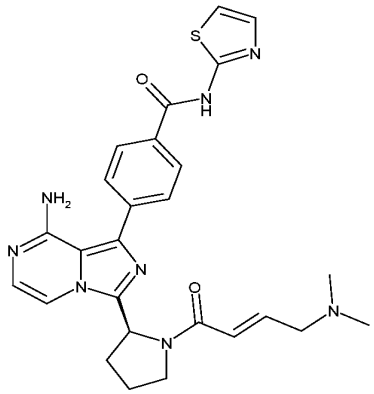
Intermediate 20



(*S*)-4-(8-Amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 2, from (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)pyrrolidine-1-carboxylate (Intermediate 1e) and commercially available N-2-thiazolyl 4-boronobenzamide to afford the title compound (229 mg, 73.1%).

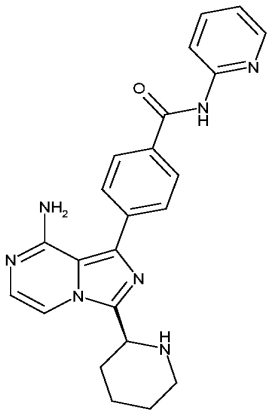
Example 15



(*S*,*E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide (intermediate 20) and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (18.9 mg, 29.7%). Data: UPLC (C) R_t : 1.38 min; *m/z* 517.3 $(M+H)^+$.

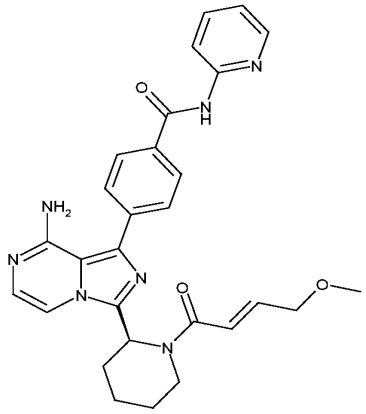
Intermediate 21



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, in an analogous manner as described for intermediate 2, afforded the title compound (491 mg, 91%).

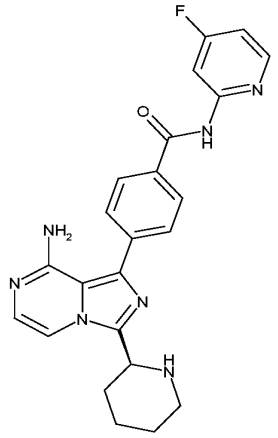
Example 16



(*S*,*E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 21) and (*E*)-4-methoxybut-2-enoic acid (intermediate 3), to afford the title compound (21.1 mg, 54.3%). Data: LCMS (B) R_t : 2.22 min; *m/z* 512.3 $(M+H)^+$.

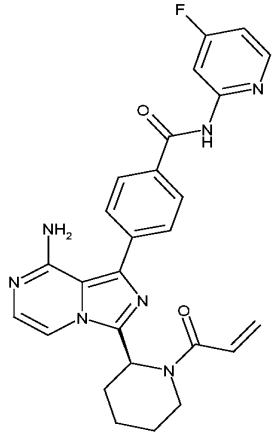
Intermediate 22



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-fluoropyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 4), in an analogous manner as described for intermediate 2, afforded the title compound (160 mg, 71.8%).

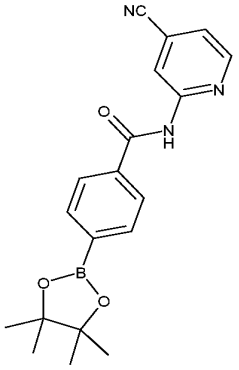
Example 17



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide (intermediate 22) and acryloylchlroide, to afford the title compound (12 mg, 42.7%). Data: UPLC(C) R_t : 2.29 min; *m/z* 486.3 $(M+H)^+$.

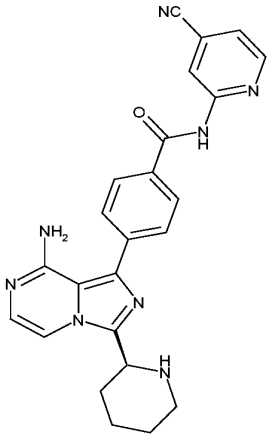
Intermediate 23



N-(4-Cyanopyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 4, starting from 2-aminoisonicotinonitrile, to afford the title compound (1.3 g, 99%).

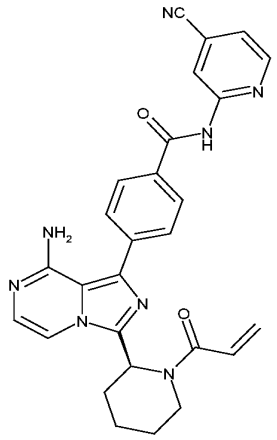
Intermediate 24



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-cyanopyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 23), in an analogous manner as described for intermediate 2, afforded the title compound (82 mg, 35.7%).

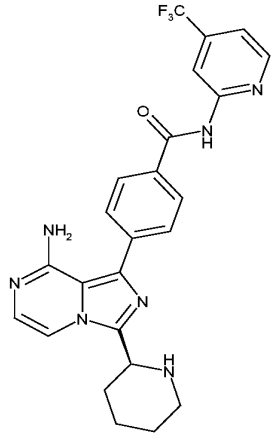
Example 18



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide (intermediate 24) and acryloylchloride, to afford the title compound (4.8 mg, 10.4%). Data: UPLC(C) R_t : 2.31 min.

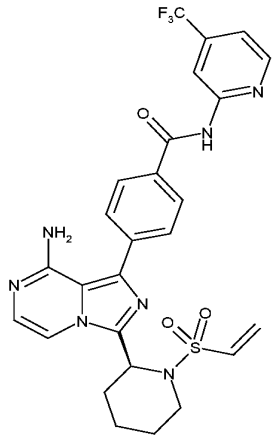
Intermediate 25



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (Intermediate 10), in an analogous manner as described for intermediate 2, afforded the title compound (144 mg, 59.1%).

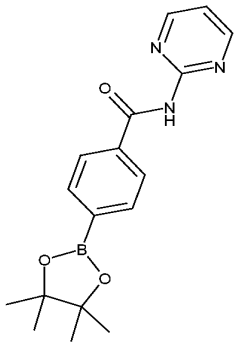
Example 19



(*S*)-4-(8-Amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 25) and ethenesulfonyl chloride prepared according to procedures described by King et.al. in Can. J. Chem. **66** (1988) pp1109-1116, to afford the title compound (6.1 mg, 20.5%). Data: UPLC(B) R_t : 1.24 min; *m/z* 572.2 $(M+H)^+$.

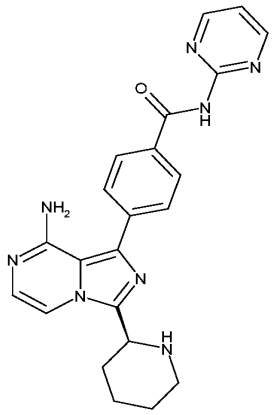
Intermediate 26



N-(Pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 2-aminopyrimidine, to afford the title compound (855 mg, 42.6%).

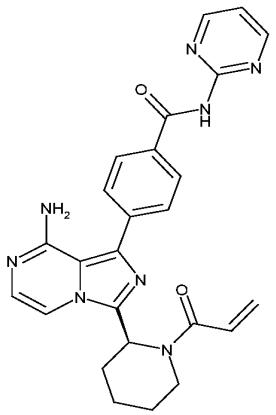
Intermediate 27



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 26), in an analogous manner as described for intermediate 2, afforded the title compound (100.8 mg, 95.4%).

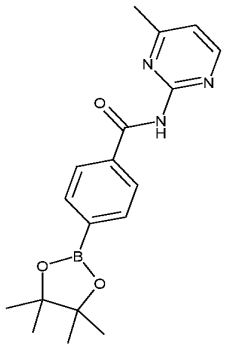
Example 20



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide (intermediate 27) and acryloylchloride, to afford the title compound (5.9 mg, 26.2%). Data: UPLC(C) R_t : 1.70 min; *m/z* 469.3 $(M+H)^+$.

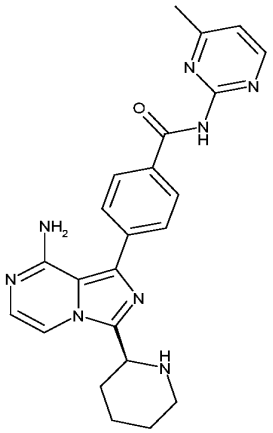
Intermediate 28



N-(4-Methylpyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 2-amino-4-methylpyrimidine, to afford the title compound (420 mg, 60.6%).

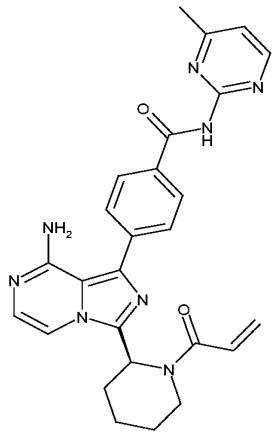
Intermediate 29



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(4-methylpyrimidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 28), in an analogous manner as described for intermediate 2, afforded the title compound (83 mg, 50.4%).

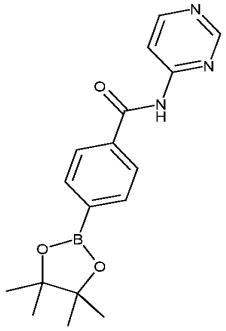
Example 21



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide (intermediate 29) and acryloylchloride, to afford the title compound (4.5 mg, 27.4%). Data: UPLC(C) R_t : 1.79 min; *m/z* 483.3 $(M+H)^+$.

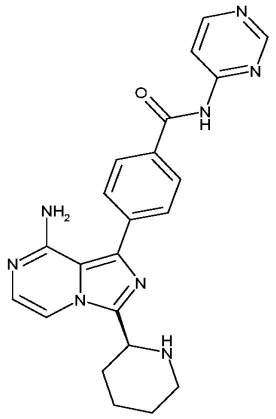
Intermediate 30



N-(Pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 4-aminopyrimidine, to afford the title compound (1 g, 59.4%).

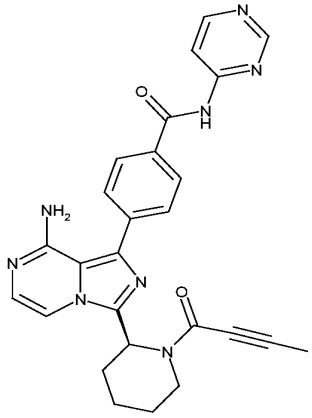
Intermediate 31



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyrimidin-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 30), in an analogous manner as described for intermediate 2, afforded the title compound (66 mg, 42.8%).

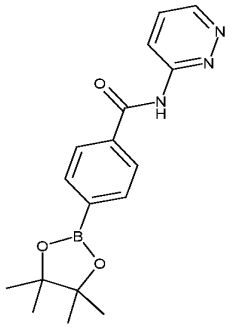
Example 22



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide (intermediate 31) and 2-butynoic acid, to afford the title compound (10.3 mg, 26.9%). Data: UPLC(C) R_t : 1.91 min; *m/z* 481.3 $(M+H)^+$.

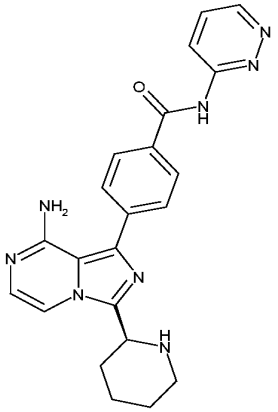
Intermediate 32



N-(Pyridazin-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 3-aminopyridazine, to afford the title compound (1.25 g, 71.3%).

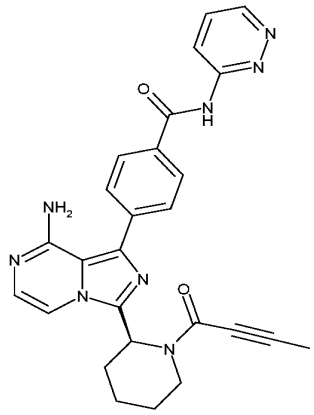
Intermediate 33



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(pyridazin-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 32) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (258 mg, 85%).

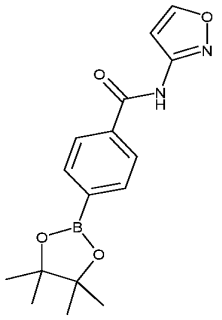
Example 23



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide (intermediate 33) and 2-butynoic acid, to afford the title compound (11 mg, 31.8%). Data: UPLC(C) R_t : 1.92 min; *m/z* 481.3 $(M+H)^+$.

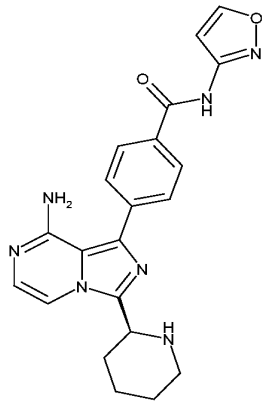
Intermediate 34



N-(Isoxazol-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from 3-aminoisoxazole, to afford the title compound (1.64 g, 95%).

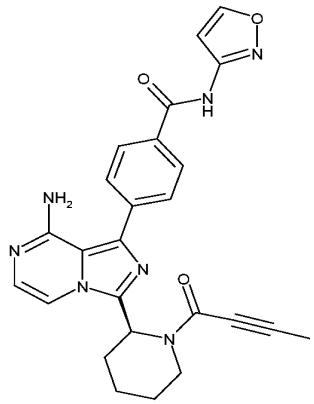
Intermediate 35



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(isoxazol-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 34) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (72 mg, 129%).

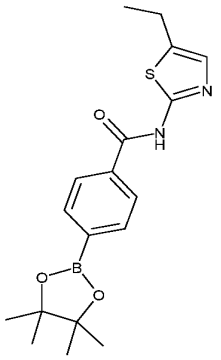
Example 24



(*S*)-4-(8-Amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide (intermediate 35) and 2-butynoic acid, to afford the title compound (2 mg, 6.6%). Data: UPLC(C) R_t : 2.23 min; *m/z* 470.3 $(M+H)^+$.

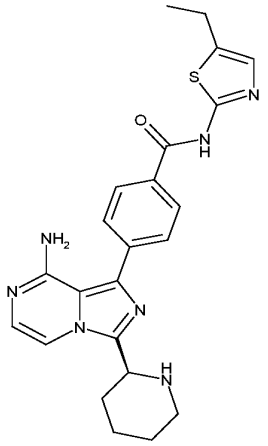
Intermediate 36



N-(5-Ethylthiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 4, starting from 5-ethylthiazol-2-amine, to afford the title compound (191 mg, 34.2%).

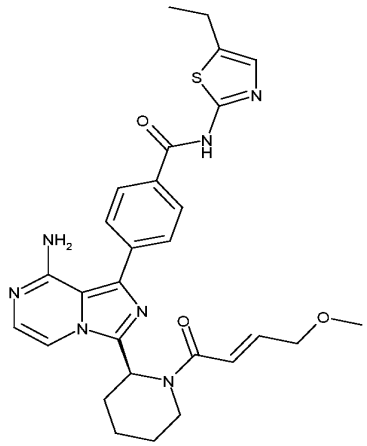
Intermediate 37



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with N-(5-ethylthiazol-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 36) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (146 mg, 52.4%).

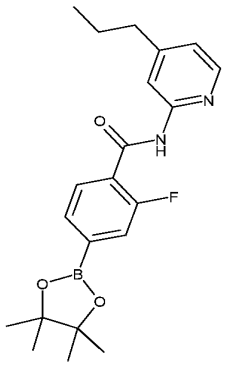
Example 25



(*S*,*E*)-4-(8-Amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide (intermediate 37) and (*E*)-4-methoxybut-2-enoic acid (Intermediate 3), to afford the title compound (11.7 mg, 47.6%). Data: UPLC(C) R_t : 2.59 min; *m/z* 546.3 $(M+H)^+$.

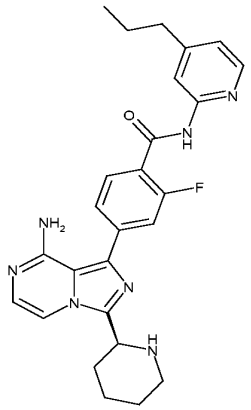
Intermediate 38



2-Fluoro-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 4, starting from commercially available 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid and 4-propyl-pyridin-2-ylamine, to afford the title compound (830 mg, 63.3%).

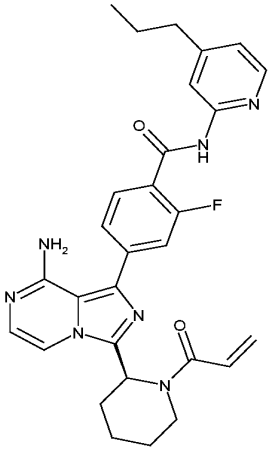
Intermediate 39



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 2-fluoro-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamid (Intermediate 38) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (75.4 mg, 62%).

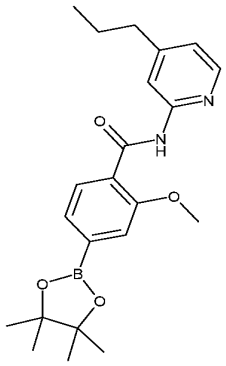
Example 26



(*S*)-4-(3-(1-Acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide (intermediate 39) and acrylic acid, to afford the title compound (5.9 mg, 28.9%). Data: UPLC(C) R_t : 2.41 min; *m/z* 528.4 $(M+H)^+$.

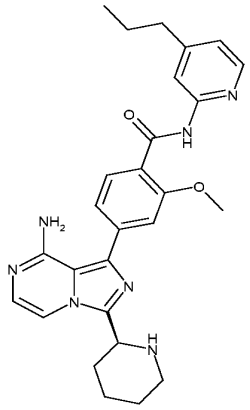
Intermediate 40



2-Methoxy-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from commercially available 4-bromo-2-methoxybenzoic acid and 4-propyl-pyridin-2-ylamine, to afford the title compound (240 mg, 15.1%).

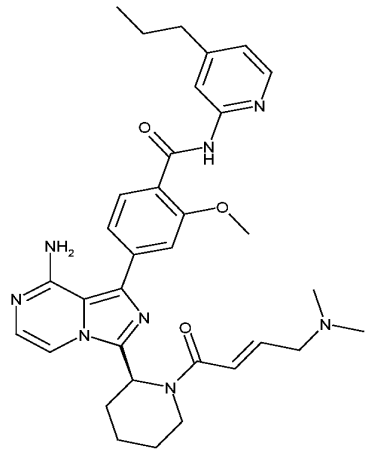
Intermediate 41



(*S*)-4-(8-Amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 2-methoxy-N-(4-propylpyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 40) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (74.5 mg, 75%).

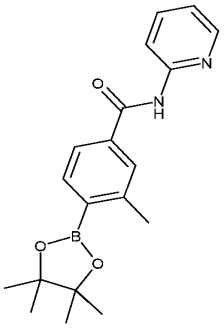
Example 27



(*S*,*E*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide (intermediate 41) and (*E*)-4-(dimethylamino)but-2-enoic acid, to afford the title compound (13.1 mg, 38.4%). Data: UPLC(C) R_t : 1.86 min; *m/z* 597.4 $(M+H)^+$.

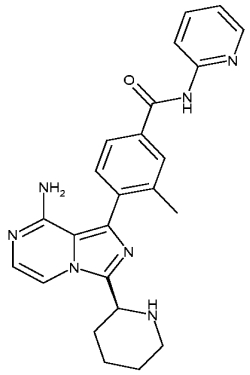
Intermediate 42



3-Methyl-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Intermediate 14, starting from commercially available 4-bromo-3-methylbenzoic acid and 2-aminopyridine, to afford the title compound (2.5 g, 71.3%).

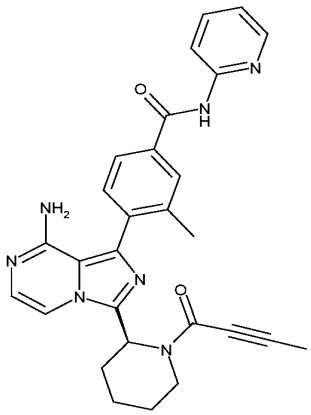
Intermediate 43



4-(8-Amino-3-((*S*)-piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-1-(benzyloxycarbonyl)piperidine-2-carboxylic acid to obtain (S)-benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate. Subsequent reaction with 3-methyl-N-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (Intermediate 42) and deprotection, in an analogous manner as described for intermediate 2, afforded the title compound (150 mg, 71.7%).

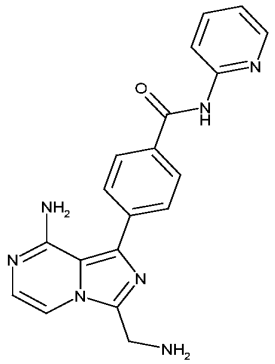
Example 28



4-(8-Amino-3-((*S*)-1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from 4-(8-amino-3-((*S*)-piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide (intermediate 43) and 2-butynoic acid, to afford the title compound (13.7 mg, 59.1%). Data: UPLC(C) R_t : 2.28 min; *m/z* 494.3 $(M+H)^+$.

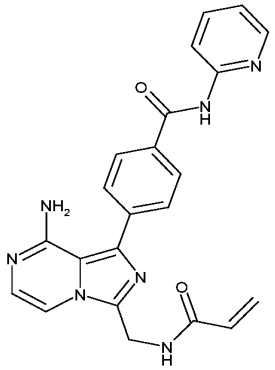
Intermediate 44



4-(8-Amino-3-(aminomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from Z-Gly-OH to obtain benzyl (8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)methylcarbamate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, in an analogous manner as described for intermediate 2, afforded the title compound (261 mg, 81%).

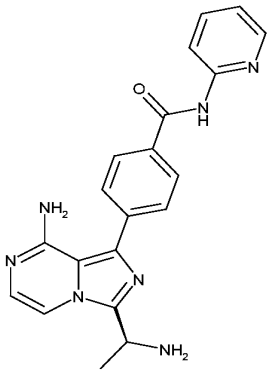
Example 29



4-(3-(Acrylamidomethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from 4-(8-amino-3-(aminomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 44) and acryloylchloride, to afford the title compound (1.7 mg, 4%). Data: UPLC(C) R_t : 1.22 min; *m/z* 414.2 $(M+H)^+$.

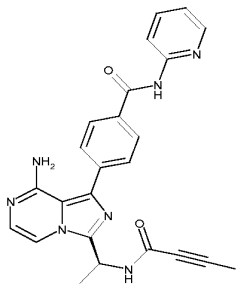
Intermediate 45



(*S*)-4-(8-Amino-3-(1-aminoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from Z-Ala-OH to obtain benzyl (*S*)-benzyl 1-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)ethylcarbamate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid and deprotection with 33%HBr/HOAc, in an analogous manner as described for intermediate 2, afforded the title compound (133.6 mg, 80%).

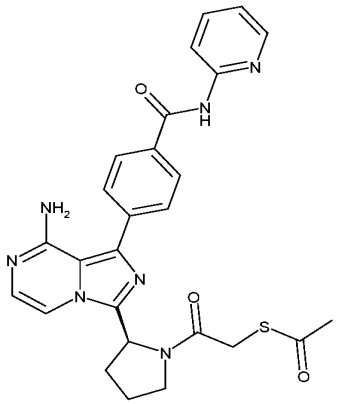
Example 30



(*S*)-4-(8-Amino-3-(1-but-2-ynamidoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(1-aminoethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 45) and 2-butynoic acid, to afford the title compound (9.5 mg, 26.9%). Data: UPLC(C) R_t : 1.38 min; *m/z* 440.3 $(M+H)^+$.

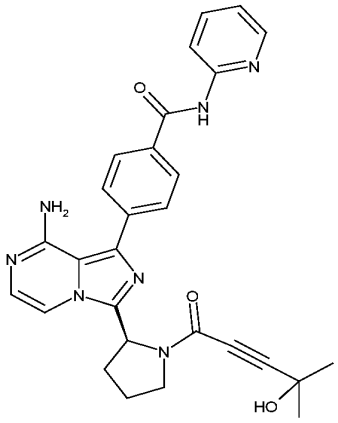
Example 31



(*S*)-S-2-(2-(8-Amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)pyrrolidin-1-yl)-2-oxoethyl ethanethioate

This compound was prepared, in an analogous manner as described in Example 1, from the compound described in intermediate 2b and 2,5-dioxopyrrolidin-1-yl 2-(acetylthio)acetate, to afford the title compound (12.3 mg, 31.8%). Data: UPLC (C) R_t : 1.51 min; *m/z* 516.3 $(M+H)^+$.

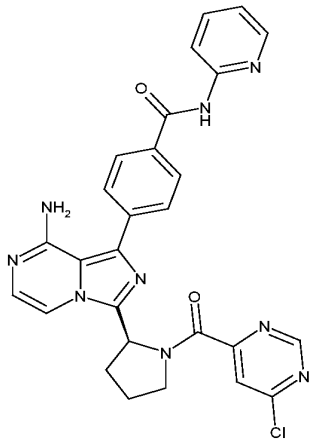
Example 32



(*S*)-4-(8-Amino-3-(1-(4-hydroxy-4-methylpent-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 4-hydroxy-4-methylpent-2-ynoic acid, to afford the title compound (8.0 mg, 25.1%). Data: UPLC (C) R_t : 1.53 min; *m/z* 510.3 $(M+H)^+$.

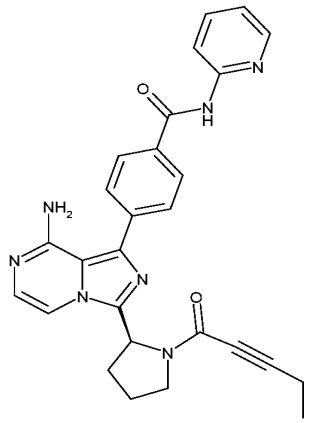
Example 33



(*S*)-4-(8-Amino-3-(1-(6-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 6-chloropyrimidine-4-carboxylic acid, to afford the title compound (2.5 mg, 6.2%). Data: UPLC (C) R_t : 1.64 min; *m/z* 540.3 $(M+H)^+$.

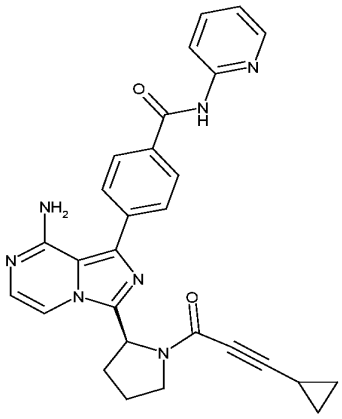
Example 34



(*S*)-4-(8-Amino-3-(1-pent-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and pent-2-ynoic acid, to afford the title compound (7.4 mg, 24.7%). Data: UPLC (C) R_t : 1.73 min; *m/z* 480.3 $(M+H)^+$.

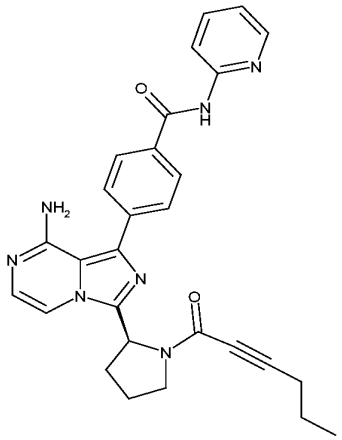
Example 35



(*S*)-4-(8-Amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 3-cyclopropylpropiolic acid, to afford the title compound (8 mg, 26%). Data: UPLC (C) R_t : 1.73 min; *m/z* 492.3 $(M+H)^+$.

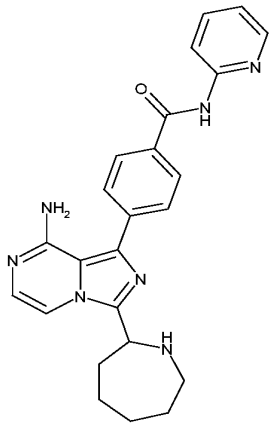
Example 36



(*S*)-4-(8-Amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and hex-2-ynoic acid, to afford the title compound (8.1 mg, 26.2%). Data: UPLC (C) R_t : 1.94 min; *m/z* 494.3 $(M+H)^+$.

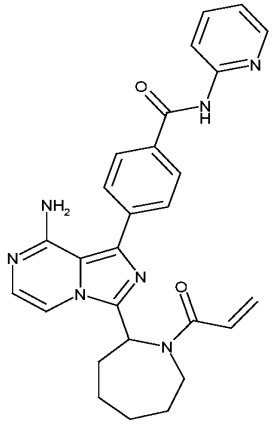
Intermediate 46



4-(8-Amino-3-(azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from 1-(benzyloxycarbonyl)azepane-2-carboxylic acid to obtain benzyl 2-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)azepane-1-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, in an analogous manner as described for intermediate 2, afforded the title compound (436 mg, quantitative, crude).

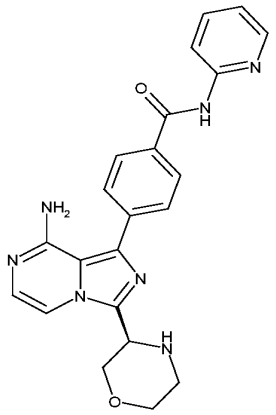
Example 37



4-(3-(1-Acryloylazepan-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 1, from 4-(8-amino-3-(azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 46) and acryloylchloride, to afford the title compound (11 mg, 32.6%). Data: UPLC(C) R_t : 1.88 min; *m/z* 482.3 $(M+H)^+$.

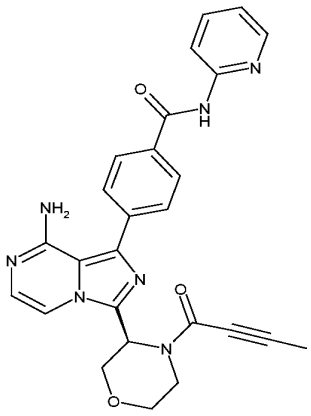
Intermediate 47



(*R*)-4-(8-Amino-3-(morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-4-(benzyloxycarbonyl)morpholine-3-carboxylic acid to obtain (*R*)-benzyl 3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)morpholine-4-carboxylate. Subsequent reaction with commercially available 4-(pyridin-2-yl-aminocarbonyl)benzeneboronic acid, in an analogous manner as described for intermediate 2, and subsequent deprotection using TFA at 60°C, afforded the title compound (62 mg, 69.5%).

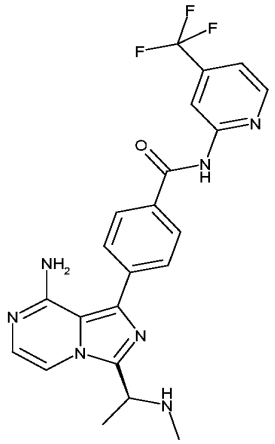
Example 38



(*R*)-4-(8-Amino-3-(4-but-2-ynoylmorpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

This compound was prepared, in an analogous manner as described in Example 2, from (*R*)-4-(8-amino-3-(morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (intermediate 47) and 2-butynoic acid, to afford the title compound (4.9 mg, 14.1%). Data: UPLC(C) R_t : 1.38 min; *m/z* 482.3 $(M+H)^+$.

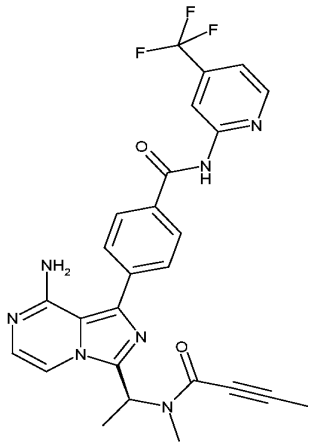
Intermediate 48



(*S*)-4-(8-Amino-3-(1-(methylamino)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

This intermediate was prepared, in an analogous manner as described for intermediate 1, from (*S*)-2-((benzyloxycarbonyl)(methyl)amino)propanoic acid to obtain (*S*)-benzyl 1-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)ethyl(methyl)carbamate. Subsequent reaction with 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (Intermediate 10), in an analogous manner as described for intermediate 2, afforded the title compound (71 mg, 64.7%).

Example 39



(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

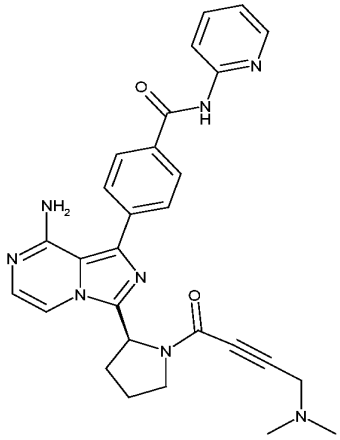
This compound was prepared, in an analogous manner as described in Example 2, from (*S*)-4-(8-amino-3-(1-(methylamino)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (intermediate 48) and 2-butynoic acid, to afford the title compound (11.5 mg, 33.4%). Data: UPLC(C) R_t : 2.54 min; *m/z* 522.2 $(M+H)^+$.

Intermediate 49

4-(Dimethylamino)but-2-ynoic acid

n-BuLi in hexane (2.5M, 24.06 mmol, 9.62 mL) was slowly added to a solution of *N,N*-dimethylprop-2-yn-1-amine (24.06 mmol, 2,59 mL, 2 g) in dry THF (10 mL) at -78°C. The mixture was stirred for 1 h at -78°C, then crushed CO_2 (241 mmol, 10.59 g) was added in one portion and the reaction mixture was stirred for an additional 10 min. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated *in vacuo* to give the crude amino acid. This was dissolved in methanol, and the insoluble salts were removed via filtration. The filtrate was evaporated to give 3.25 g of 4-(dimethylamino)but-2-ynoic acid (106%).

Example 40



(*S*)-4-(8-Amino-3-(1-(4-(dimethylamino)but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

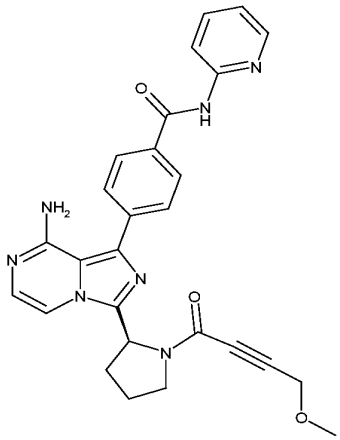
This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 4-(dimethylamino)but-2-ynoic acid (Intermediate 49), to afford the title compound (5.6 mg, 12%). Data: UPLC (C) R_t : 0.97 min; *m/z* 509.3 $(M+H)^+$.

Intermediate 50

4-Methoxybut-2-ynoic acid

n-BuLi in hexane (2.5M, 28.5 mmol, 11.41 mL) was slowly added to a solution of 3-methoxyprop-1-yne (28.5 mmol, 2,41 mL, 2 g) in dry THF (10 mL) at -78°C. The mixture was stirred for 1 h at -78°C, then crushed CO_2 (285 mmol, 12.56 g) was added in one portion and the reaction mixture was stirred for an additional 10 min. The resulting solution was poured into water and washed with ethyl acetate. The aqueous layer was evaporated *in vacuo* to give the crude amino acid. This was dissolved in methanol, and the insoluble salts were removed via filtration. The filtrate was evaporated to give 3.35 g of 4-methoxybut-2-ynoic acid (103%).

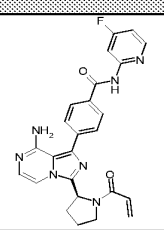
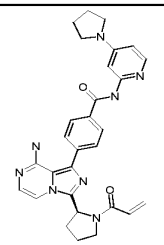
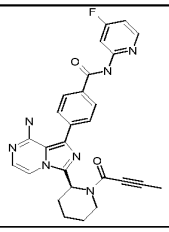
Example 41

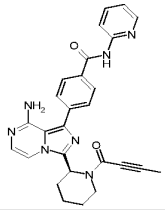
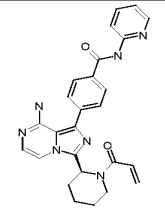
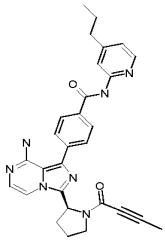
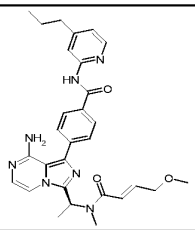
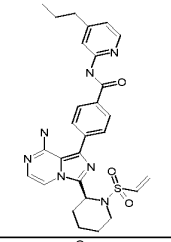
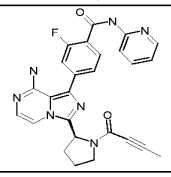


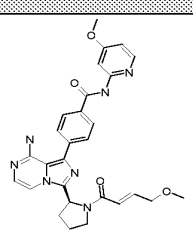
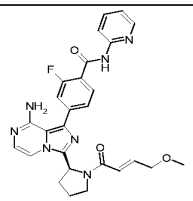
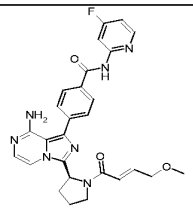
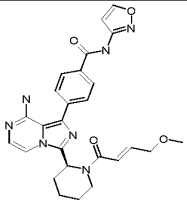
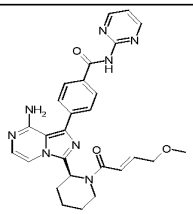
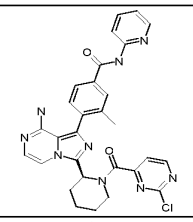
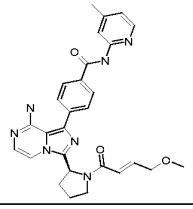
(*S*)-4-(8-Amino-3-(1-(4-methoxybut-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

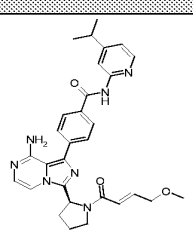
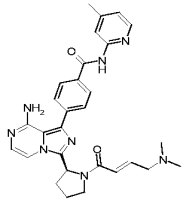
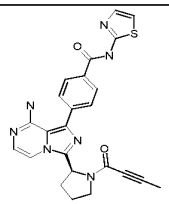
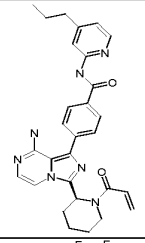
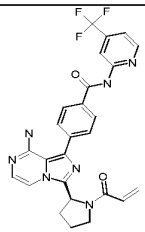
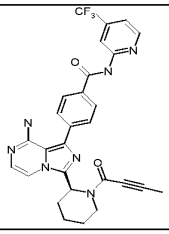
This compound was prepared, in an analogous manner as described in Example 2, from the compound described in intermediate 2b and 4-methoxybut-2-ynoic acid (Intermediate 50), to afford the title compound (9.1 mg, 24.7%). Data: UPLC (C) R_t : 1.44 min; *m/z* 496.2 $(M+H)^+$.

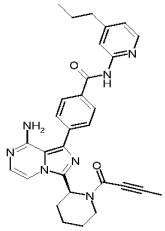
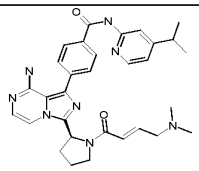
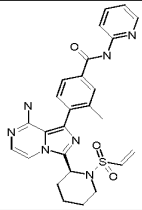
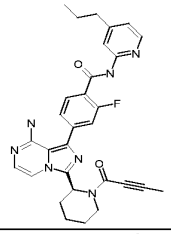
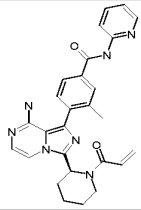
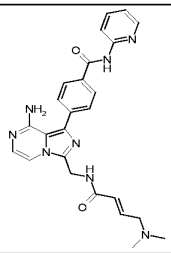
The following Examples were synthesized following the methods described for example 1-41.

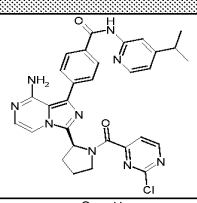
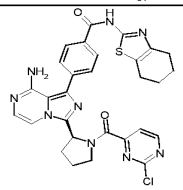
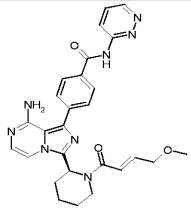
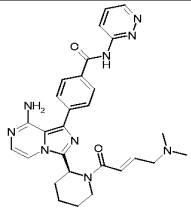
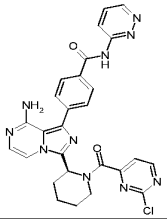
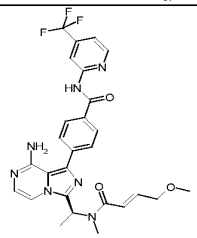
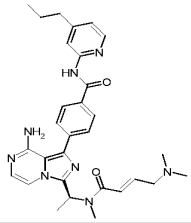
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
42		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	472.3	2.25 min
43		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide	523.3	1.72 min
44		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	498.3	2.47 min

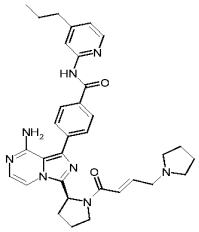
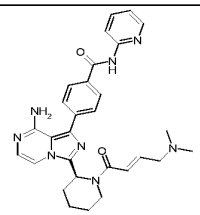
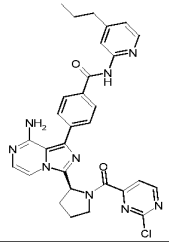
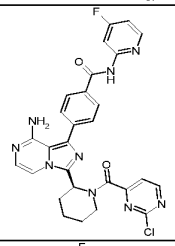
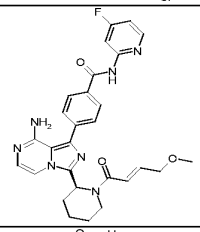
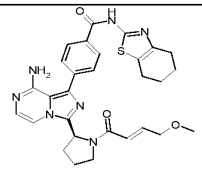
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
45		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	480.3	2.26 min LCMS (B)
46		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.3	2.49 min
47		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	508.3	2.00 min
48		(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	528.3	1.89 min
49		(*S*)-4-(8-amino-3-(1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	546.3	2.15 min
50		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide	484.3	1.84 min

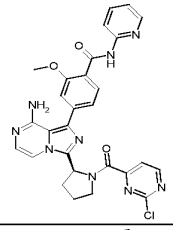
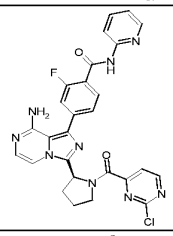
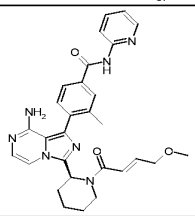
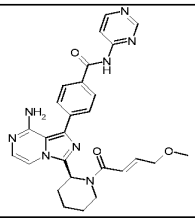
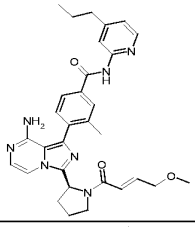
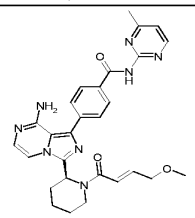
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
51		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide	528.4	1.60 min
52		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-methoxypyridin-2-yl)benzamide	516.3	1.79 min
53		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	516.3	2.31 min
54		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(isoxazol-3-yl)benzamide	502.3	2.01 min
55		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide	513.3	1.79 min
56		4-(8-amino-3-((*S*)-1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	568.3	2.23 min
57		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	512.4	1.67 min

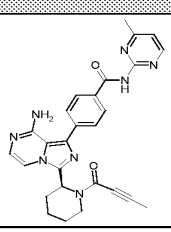
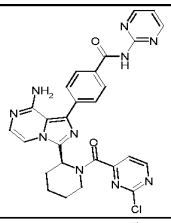
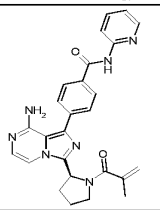
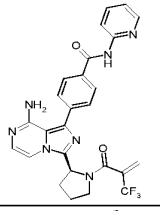
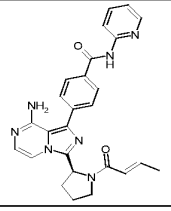
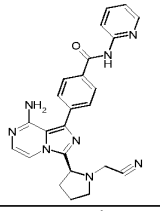
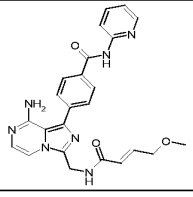
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
58		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	540.3	1.74 min
59		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	525.4	1.11 min
60		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	472.0	2.24 min
61		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	510.3	2.11 min
62		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	522.0	2.37 min
63		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	548.3	1.09 min UPLC (B)

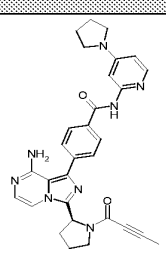
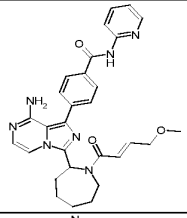
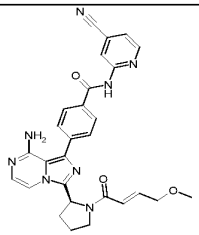
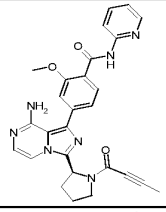
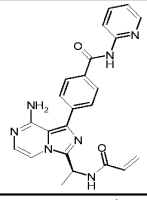
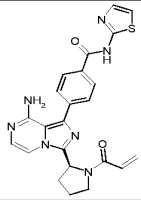
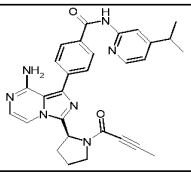
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
64		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	522.3	2.29 min
65		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	553.3	1.31 min
66		4-(8-amino-3-((*S*)-1-(vinylsulfonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	518.3	2.20 min
67		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	540.3	2.56 min
68		4-(3-((*S*)-1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	482.2	1.98 min
69		(*E*)-4-(8-amino-3-((4-(dimethyl amino)but-2-enamido)methyl) imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	471.2	1.16 min

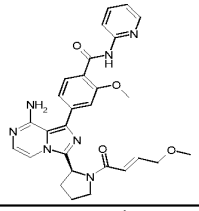
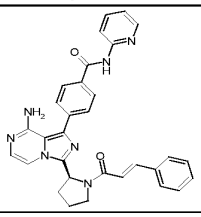
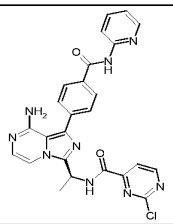
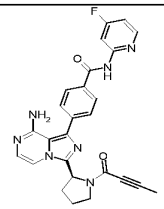
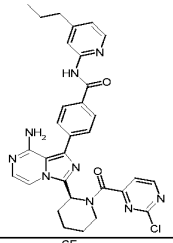
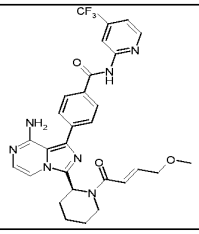
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
70		(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	582.2	1.89 min
71		(*S*)-4-(8-amino-3-(1-(2-chloro pyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	600.2	2.49 min
72		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	513.3	1.84 min
73		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	526.4	1.26 min
74		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridazin-3-yl)benzamide	555.3	1.96 min
75		(*S,E*)-4-(8-amino-3-(1-(4-methoxy-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	554.2	2.47 min
76		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)-N-methylbut-2-enamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	541.3	1.41 min

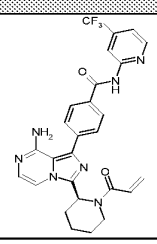
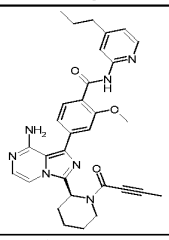
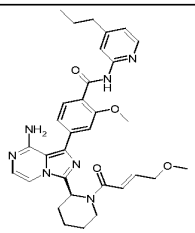
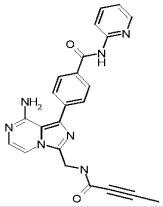
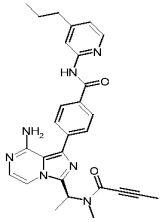
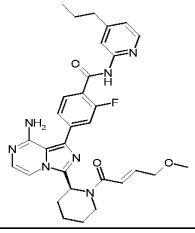
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
77		(*S,E*)-4-(8-amino-3-(1-(4-(pyrrolidin-1-yl)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	579.3	1.64 min
78		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	525.3	2.10 min LCMS (B)
79		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	582.3	1.95 min
80		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	572.3	2.45 min
81		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	530.3	2.38 min
82		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)benzamide	558.3	2.33 min

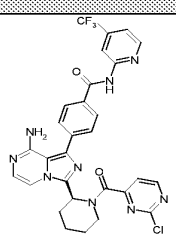
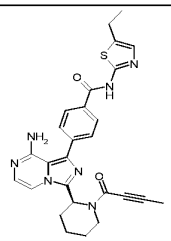
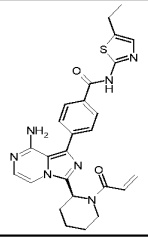
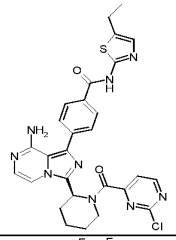
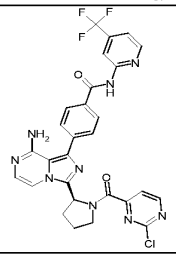
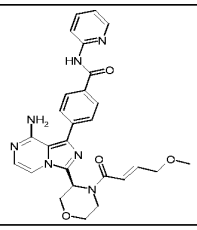
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
83		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	570.3	2.01 min
84		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(pyridin-2-yl)benzamide	558.2	1.95 min
85		4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(pyridin-2-yl)benzamide	526.3	2.12 min
86		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-4-yl)benzamide	513.3	1.83 min
87		4-(8-amino-3-((*S*)-1-((*E*)-4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-3-methyl-N-(4-propylpyridin-2-yl)benzamide	554.4	1.86 min
88		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide	527.3	1.88 min

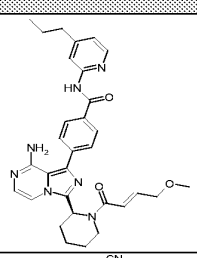
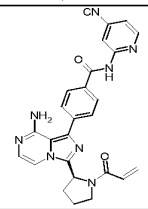
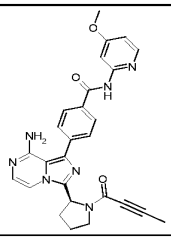
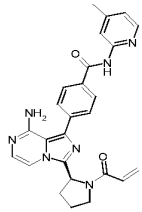
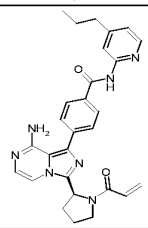
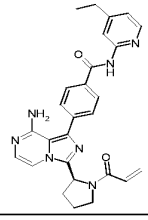
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
89		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyrimidin-2-yl)benzamide	495.3	1.97 min
90		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyrimidin-2-yl)benzamide	555.3	1.91 min
91		(*S*)-4-(8-amino-3-(1-methacryloylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.4	1.61 min
92		(*S*)-4-(8-amino-3-(1-(2-(trifluoromethyl)acryloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	522.3	1.99 min
93		(*S,E*)-4-(8-amino-3-(1-but-2-enoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	468.4	1.59 min
94		(*S*)-4-(8-amino-3-(1-(cyanomethyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	439.3	1.55 min
95		(*E*)-4-(8-amino-3-((4-methoxybut-2-enamido)methyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	458.2	1.35 min

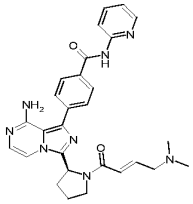
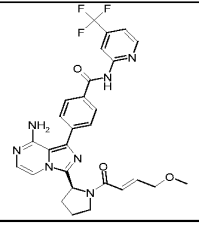
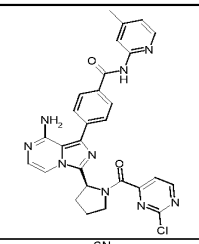
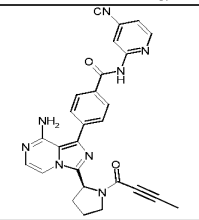
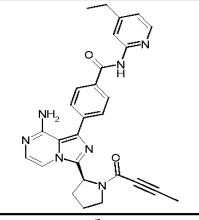
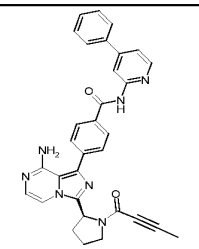
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
96		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(pyrrolidin-1-yl)pyridin-2-yl)benzamide	535.3	2.27 min LCMS (B)
97		(*E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)azepan-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	526.3	1.97 min
98		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	523.3	2.12 min
99		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	496.3	1.87 min
100		(*S*)-4-(3-(1-acrylamidoethyl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	428.3	1.15 min
101		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(thiazol-2-yl)benzamide	460.2	2.03 min
102		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-isopropylpyridin-2-yl)benzamide	507.8	1.82 min

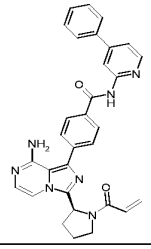
Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
103		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide	528.3	1.84 min
104		(*S,E*)-4-(8-amino-3-(1-cinnamoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	530.4	2.09 min
105		(*S*)-N-(1-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)ethyl)-2-chloropyrimidine-4-carboxamide	514.3	1.56 min
106		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-fluoropyridin-2-yl)benzamide	484.2	2.38 min
107		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	596.3	2.19 min
108		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	580.3	1.03 min UPLC (B)

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
109		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	536.3	1.02 min UPLC (B)
110		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	552.4	2.57 min
111		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(4-propylpyridin-2-yl)benzamide	584.4	2.49 min
112		4-(8-amino-3-(but-2-ynamidomethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	426.2	1.35 min
113		(*S*)-4-(8-amino-3-(1-(N-methylbut-2-ynamido)ethyl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	496.3	1.94 min
114		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-fluoro-N-(4-propylpyridin-2-yl)benzamide	572.4	2.48 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
115		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	622.2	1.15 min UPLC (B)
116		(*S*)-4-(8-amino-3-(1-but-2-ynoylpiperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	514.3	2.68 min
117		(*S*)-4-(3-(1-acryloylpiperidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	502.3	2.53 min
118		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(5-ethylthiazol-2-yl)benzamide	588.3	2.71 min
119		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	608.2	2.68 min
120		(*R,E*)-4-(8-amino-3-(4-(4-methoxybut-2-enoyl)morpholin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	514.3	1.34 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
121		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)piperidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	554.4	2.07 min
122		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	479.0	1.86 min
123		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methoxypyridin-2-yl)benzamide	496.3	1.50 min
124		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	468.1	1.37 min
125		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-propylpyridin-2-yl)benzamide	496.1	1.76 min
126		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	482.1	1.53 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
127		(*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide	511.0	1.29 min
128		(*S,E*)-4-(8-amino-3-(1-(4-methoxybut-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide	566.3	2.73 min
129		(*S*)-4-(8-amino-3-(1-(2-chloropyrimidine-4-carbonyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-methylpyridin-2-yl)benzamide	554.2	1.38 min
130		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-cyanopyridin-2-yl)benzamide	491.2	2.20 min
131		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-ethylpyridin-2-yl)benzamide	494.3	1.65 min
132		(*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	542.3	2.57 min

Example	Structure	Name	(M+H)+ m/z	UPLC (C) Rt
133		(*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(4-phenylpyridin-2-yl)benzamide	530.3	2.38 min

Example 134 Assay Methods

Btk enzyme activity

Btk enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Btk enzyme (His-Btk (Millipore catalog# 14-552), is diluted to 0.4 U/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer. Final compound concentration range in the assay from 10 μM to 0.316 nM.

5 μL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 μl/well of 0.4 U/mL Btk enzyme (final concentration in the assay is 0.1 U/mL). Test compounds and Btk enzyme are pre-incubated 60 minutes at room temperature, before adding 5 μL/well of 200 nM Fluorescin labeled substrate peptide (Blk/Lyntide substrate, e.g. #R7188/#R7233, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 50 nM. The kinase assay is started by adding 5 μL/well of 20 μM ATP in KR-buffer (final ATP concentration is 5 μM ATP, Km ATP in Btk IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 μL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

All examples have an EC50 of 10 μM or lower.

Table 1 EC50 Btk activity values	
EC50	**Example**
≥1μM	91,
≥100nM <1μM	52, 53, 54, 55, 68, 72, 74, 85, 86, 87, 88, 90, 92, 93, 94, 104
≥10nM <100nM	2, 4, 5, 7, 11, 24, 40, 41, 50, 51, 56, 57, 58, 59, 60, 69, 70, 71, 73, 80, 81, 82, 83, 84, 89, 95, 96, 97, 98, 99, 103, 105, 106, 112, 113, 114, 119
<10 nM	1, 3, 6, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 61, 62, 63, 64, 65, 66, 67, 75, 76, 77, 78, 79, 100, 101, 102, 107, 108, 109, 110, 111, 115, 116, 117, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

Lck enzyme activity

Lck enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Lck enzyme (Millipore catalog# 14-442), is diluted to 0.4 U/mL in KR buffer (10 mM Tris-HCl, 10 mM MgCl2, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 µl is used in the assay, leading to a final compound concentration range in the assay from 10 µM to 0.316 nM.

5 µL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 µl/well of 0.4 U/mL Lck enzyme (final concentration in the assay is 0.1 U/mL). Test compounds and Lck enzyme are pre-incubated 60 minutes at room temperature, before adding 5 µL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 µL/well of 24 µM ATP in KR-buffer (final ATP concentration is 6 µM ATP, Km ATP in Lck IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 µL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 2 EC50 Lck activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 123, 127, 128, 129, 130, 131
≥100nM <1μM	60, 62, 64, 76, 104, 122, 124, 125, 126, 132, 133

Src enzyme activity

Src enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Src enzyme (Millipore catalog# 14-326), is diluted to 0.8 U/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 µl is used in the assay, leading to a final compound concentration range in the assay from 10 µM to 0.316 nM.

5 µL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 µl/well of 0.8 U/mL Src enzyme (final concentration in the assay is 0.2 U/mL). Test compounds and Src enzyme are pre-incubated 60 minutes at room temperature, before adding 5 µL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 µL/well of 16 µM ATP in KR-buffer (final ATP concentration is 4 µM ATP, Km ATP in Src IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 µL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 3 EC50 Src activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

FynT enzyme activity

FynT enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

FynT enzyme (Biomol catalog# SE-287), is diluted to 0.5 μg/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 μl is used in the assay, leading to a final compound concentration range in the assay from 10 μM to 0.316 nM.

5 μL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 μl/well of 0.5 μg/mL FynT enzyme (final concentration in the assay is 125 ng/mL). Test compounds and FynT enzyme are pre-incubated 60 minutes at room temperature, before adding 5 μL/well of 400 nM Fluorescin labeled substrate peptide (p34cdc2 substrate peptide, e.g. #R7157/#R7172, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 μL/well of 0.8 μM ATP in KR-buffer (final ATP concentration is 0.2 μM ATP, Km ATP in FynT IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 μL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 4 EC50 FynT activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133

Lyn enzyme activity

Lyn enzyme activity is measured using the IMAP (immobilized metal ion affinity-based fluorescence polarization) assay as outlined below.

Lyn enzyme (Millipore catalog# 14-510), is diluted to 250 mU/mL in KR buffer (10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3, 1 mM DTT, 2 mM $MnCl_2$, pH 7.2).

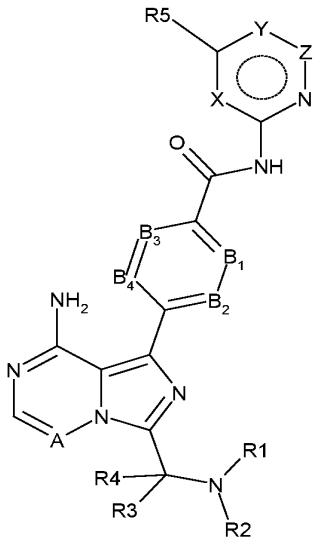
Serial dilution log10 from 2 mM to 63.2 nM of test compounds are made in 100% DMSO. The dilutions in DMSO are then diluted 50-fold in KR-buffer of which 5 µl is used in the assay, leading to a final compound concentration range in the assay from 10 µM to 0.316 nM.

5 µL/well of test compound in KR buffer (final DMSO concentration in the assay is 1%) is mixed with 5 µl/well of 250 mU/mL Lyn enzyme (final concentration in the assay is 62.5 mU/mL). Test compounds and Lyn enzyme are pre-incubated 60 minutes at room temperature, before adding 5 µL/well of 400 nM Fluorescin labeled substrate peptide (Blk/Lyntide substrate, e.g. #R7188/#R7233, Molecular Devices) in KR-buffer. Final peptide substrate concentration in assay is 100 nM. The kinase assay is started by adding 5 µL/well of 8 µM ATP in KR-buffer (final ATP concentration is 2 µM ATP, Km ATP in Lyn IMAP assay). Following incubation for 2h at room temperature the enzyme reaction is stopped by adding 40 µL/well IMAP Progressive Binding Solution (according to suppliers (Molecular Devices) protocol using 75% 1x buffer A and 25% 1x buffer B with 1:600 Progressive Binding Solution). After 60 min incubation at room temperature in the dark the FP signal is read. Fluorescence at 535 nm is measured using parallel and perpendicular filters to determine differences in rotation due to binding of the phosphorylated substrate peptide to the beads. Values are calculated as percentage of the difference in readout (ΔmPi) of the controls with and without ATP. EC_{50} values are determined by curve fitting of the experimental results using Activity Base.

Table 5 EC50 Lyn activity values	
EC50	**Example**
≥1μM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 127, 128, 129, 130, 131, 132
≥100nM <1μM	60, 124, 125, 126, 133

Claims

1. A method for treating a Bruton's Tyrosine Kinase (Btk) mediated disorder in a subject comprising administering to the subject a compound of Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof,

in an amount effective to treat the Btk mediated disorder, thereby treating the subject,

wherein:

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or a bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO_2 or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, halogen or (1-3C)alkoxy;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the carbon atom they are attached to a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, halogen or (1-3C)alkoxy;

R10 is H, halogen or (1-3C)alkoxy;

R11 is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R12 and R13 are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from the group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;

- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y cannot be O or S;
- when Z is CH or N then Y is C(R6) or N and X is CH or N; and
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

2. The method of claim 1, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis, spondylitis, glomerulonephritis with nephrotic syndrome, glomerulonephritis without nephrotic syndrome, autoimmune hematologic disorders, hemolytic anemia, aplastic anemia, idiopathic thrombocytopenia, neutropenia, autoimmune gastritis, autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, scleroderma, type I diabetes, type II diabetes, acute active hepatitis, chronic active hepatitis, pancreatitis, primary biliary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosis, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis, Behcet's disease, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, chronic obstructive pulmonary disease, a proliferative diseases, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma, a proliferative mast cell disease, and a bone disorder related to multiple myeloma.

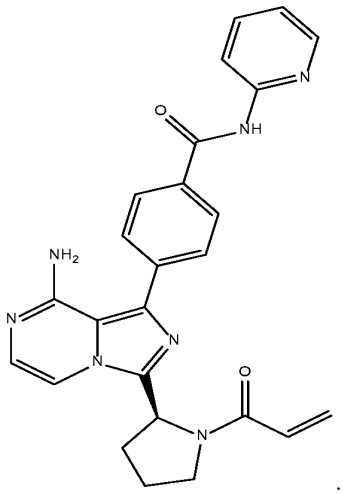
3. The method of claim 1, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, and osteoarthritis.

4. The method of claim 1, wherein the Btk mediated disorder is selected from the group consisting of a proliferative disease, non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, acute lymphoblastic leukemia, acute lymphoblastic leukemia with mature B cell, B cell lymphoma, a proliferative mast cell disease, and a bone disorder related to multiple myeloma.

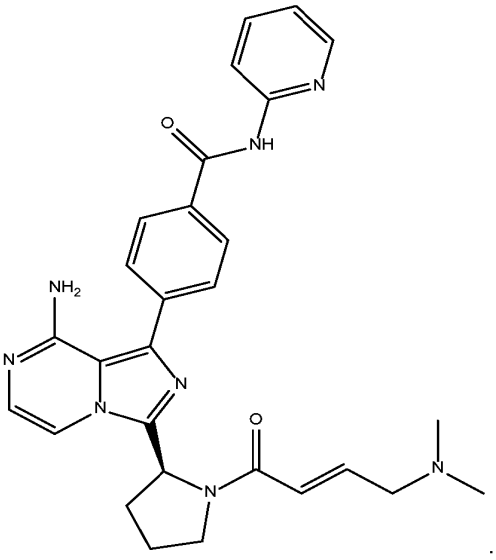
4. The method of claim 1, wherein the Btk mediated disorder is selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), B cell chronic lymphocytic leukemia, follicular lymphoma, multiple myeloma, and anemia.

5. The method of claim 1, wherein the Btk mediated disorder is a B cell malignancy.

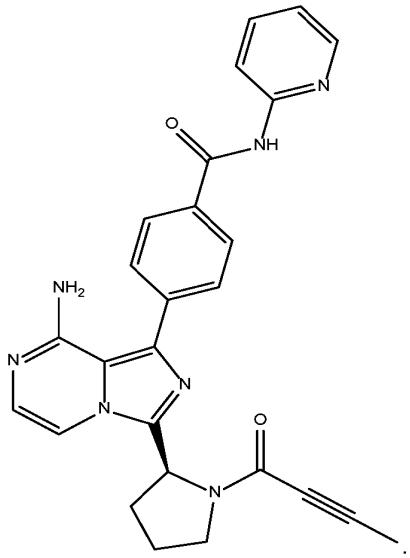
6. The method of claim 1, wherein the compound of Formula (I) is (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



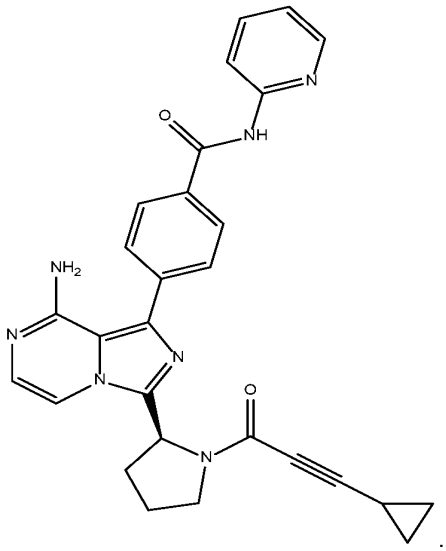
7. The method of claim 1, wherein the compound of Formula (I) is (*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



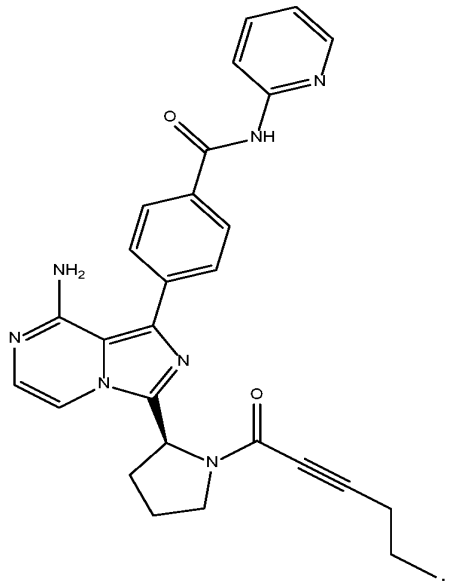
8. The method of claim 1, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



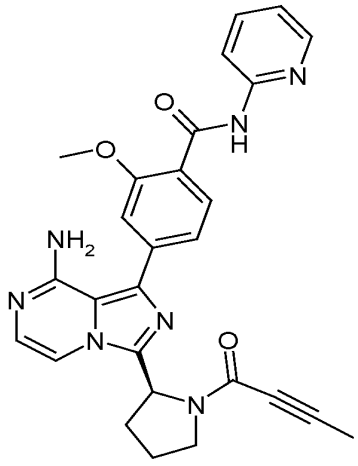
9. The method of claim 1, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



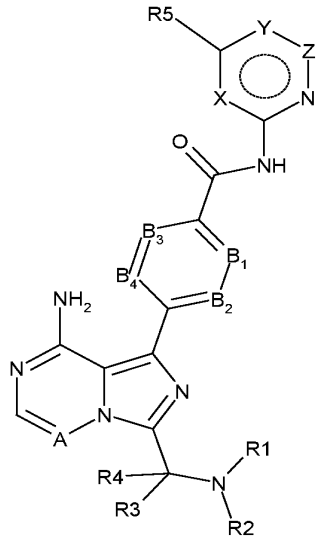
10. The method of claim 1, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



11. The method of claim 1, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide, having the structure:



12. A combination of a compound of Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof, and a further therapeutic agent,

wherein:

X is CH, N, O or S;

Y is C(R6), N, O or S;

Z is CH, N or a bond;

A is CH or N;

B1 is N or C(R7);

B2 is N or C(R8);

B3 is N or C(R9);

B4 is N or C(R10);

R1 is R11C(O), R12S(O), R13SO_2 or (1-6C)alkyl optionally substituted with R14;

R2 is H, (1-3C)alkyl or (3-7C)cycloalkyl;

R3 is H, (1-6C)alkyl or (3-7C)cycloalkyl); or

R2 and R3 form, together with the N atom that R2 is attached to and the C atom that R3 is attached to, a (3-7C)heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (1-3C)alkyl, (1-3C)alkoxy or oxo;

R4 is H or (1-3C)alkyl;

R5 is H, halogen, cyano, (1-4C)alkyl, (1-3C)alkoxy, (3-6C)cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R5 is (6-10C)aryl or (2-6C)heterocycloalkyl;

R6 is H or (1-3C)alkyl; or

R5 and R6 together may form a (3-7C)cycloalkenyl, or (2-6C)heterocycloalkenyl; each optionally substituted with (1-3C)alkyl, or one or more halogen;

R7 is H, halogen or (1-3C)alkoxy;

R8 is H or (1-3C)alkyl; or

R7 and R8 form, together with the carbon atom they are attached to a (6-10C)aryl or (1-9C)heteroaryl;

R9 is H, halogen or (1-3C)alkoxy;

R10 is H, halogen or (1-3C)alkoxy;

R11 is independently selected from the group consisting of (1-6C)alkyl, (2-6C)alkenyl and (2-6C)alkynyl each alkyl, alkenyl or alkynyl optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

R11 is (1-3C)alkyl-C(O)-S-(1-3C)alkyl; or

R11 is (1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R12 and R13 are independently selected from the group consisting of (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl or (3-7C)heterocycloalkyl; or

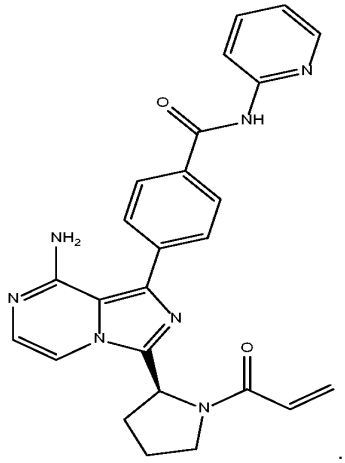
(1-5C)heteroaryl optionally substituted with one or more groups selected from halogen or cyano;

R14 is independently selected from the group consisting of halogen, cyano or (2-6C)alkenyl or (2-6C)alkynyl both optionally substituted with one or more groups selected from hydroxyl, (1-4C)alkyl, (3-7C)cycloalkyl, [(1-4C)alkyl]amino, di[(1-4C)alkyl]amino, (1-3C)alkoxy, (3-7C)cycloalkoxy, (6-10C)aryl, (1-5C)heteroaryl or (3-7C)heterocycloalkyl;

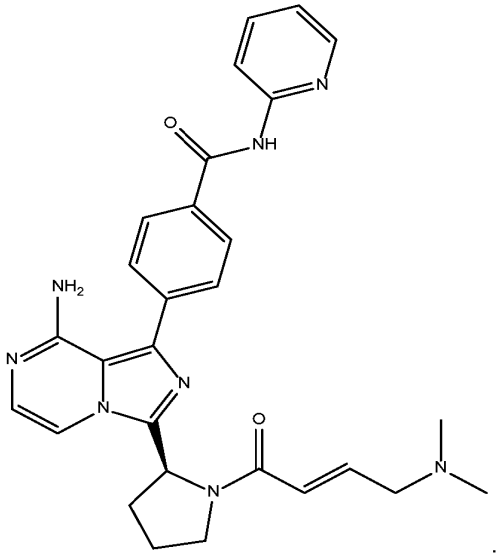
with the proviso that

- 0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;
- when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y cannot be O or S;
- when Z is CH or N then Y is C(R6) or N and X is CH or N; and
- 0 to 2 atoms of B1, B2, B3 and B4 are N.

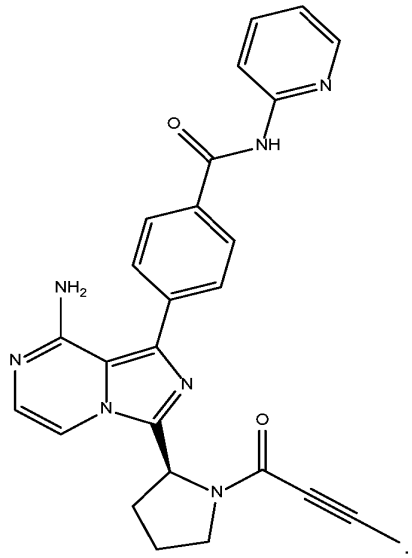
13. The combination of claim 12, wherein the compound of Formula (I) is (*S*)-4-(3-(1-acryloylpyrrolidin-2-yl)-8-aminoimidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



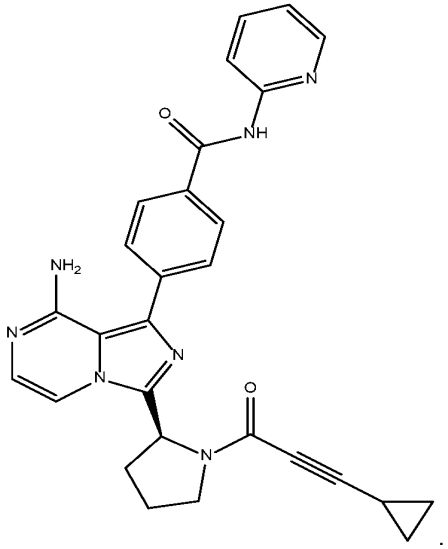
14. The combination of claim 12, wherein the compound of Formula (I) is (*S,E*)-4-(8-amino-3-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



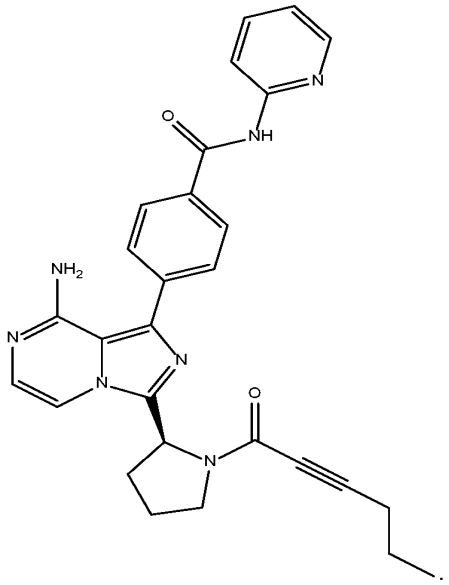
15. The combination of claim 12, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



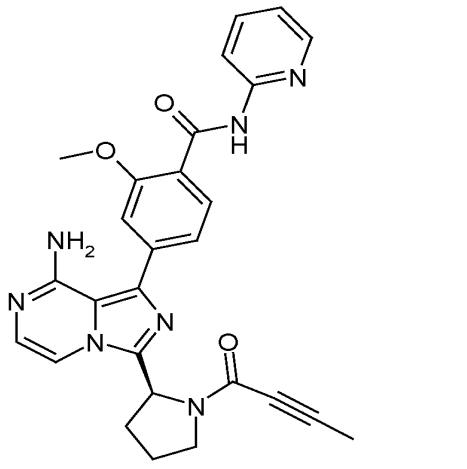
16. The combination of claim 12, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-(3-cyclopropylpropioloyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:



17. The combination of claim 12, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-hex-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide, having the structure:

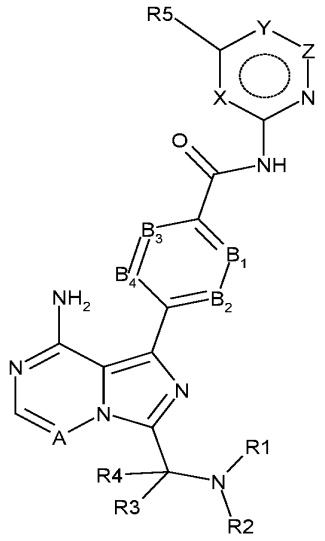


18. The combination of claim 12, wherein the compound of Formula (I) is (*S*)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-2-methoxy-N-(pyridin-2-yl)benzamide, having the structure:



Abstract

The present invention relates to 6-5 membered fused pyridine ring compounds according to Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof or to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of 6-5 membered fused pyridine ring compounds according to Formula (I) in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

Application Data Sheet

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Correspondence Information

Correspondence Customer Number::	26853

Application Information

Application Type::	Regular
Subject Matter::	Utility

CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
Attorney Docket Number::	015332.1182-US02
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	No
Petition included?::	No
Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2::	No
This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013::	No

Representative Information

Representative Customer Number::	26853

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Division of	14/233,418	01/17/14
14/233,418	National Stage of	PCT/EP2012/063552	07/11/12
PCT/EP2012/063552	An application claiming the benefit under 35 USC 119(e)	61/509,397	07/19/11

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::	DAS Access::
European Patent Office	11174578.2	07/19/11	Yes	

Applicant Information

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Country of mailing address::	Netherlands
Postal or Zip Code of mailing address::	2031 BN

Assignee Information Including Non-Applicant Assignee Information

Authorization or Opt-Out of Authorization to Permit Access

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

[x] A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

[x] B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature		Date (YYYY-MM-DD)	2016-02-09
Name	Melody H. Wu	Registration Number	52,376

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: Divisional of 14/233,418

Confirmation No.: Not Yet Assigned

Filed: February 9, 2016

Art Unit: Not Yet Assigned

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS

Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT

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

Dear Sir:

Listed on the accompanying Form PTO/SB/08, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97, and 1.98, are documents that may be considered material to the examination of this application.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date that the month of publication is not at issue. Applicant has listed publication dates on the attached Form PTO/SB/08 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited by or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

Applicant has checked the appropriate boxes below.

☒ 1. This Information Disclosure Statement is being filed within three months of the U.S. filing date OR before the mailing date of a first Office Action on the merits. No statement under 37 C.F.R. § 1.97(e) or fee is required.

☐ 2. This Information Disclosure Statement is being filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of a Final Rejection or Notice of Allowance. Attached is our Check No. _____ in the amount of $ _____ in payment of the fee under 37 C.F.R. § 1.17(p).

- ☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).
- ☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any

individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 3. This Information Disclosure Statement is being filed more than three months after the U.S. filing date and after the mailing date of a Final Rejection or Notice of Allowance, but before payment of the Issue Fee. It is hereby requested that the Information Disclosure Statement be considered. Attached is our Check No. _____ in the amount of $ _____ in payment of the fee under 37 C.F.R. § 1.17(i).

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 4. This Information Disclosure Statement is being filed more than three months after the U.S. filing date, but before the mailing of a first Office Action on the merits AFTER the filing of a Request for Continued Examination under 37 C.F.R. § 1.97(b)(4). It is hereby requested that the Information Disclosure Statement be considered. Attached is our Check No. _____ in the amount of $ _____ in payment of the fee under 37 C.F.R. § 1.17(i).

☐ a. I hereby state that each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(1).

☐ b. I hereby state that no item of information in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign

application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement. 37 C.F.R. § 1.97(e)(2).

☐ 5. Relevance of the non-English language document(s) is discussed in the present specification.

☐ 6. The document(s) was/were cited in a corresponding foreign application. An English language version of the foreign search report is attached for the Examiner's information.

☐ 7. A concise explanation of the relevance of the non-English language document(s) appears below:

☐ 8. The Examiner's attention is directed to co-pending U.S. Patent Application No. _____, filed _____, which is directed to related technical subject matter. The identification of this U.S. Patent Application is not to be construed as a waiver of secrecy as to that application now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited application, the rejection(s) made therein, and the art cited therein during examination.

☐ 9. In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. Patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

☒ 10. The listed documents were cited by or submitted to the Office in Application No. 14/233,418, filed January 17, 2014, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of the listed documents are not attached. 37 C.F.R. § 1.98(d).

It is respectfully requested that the Examiner initial and return a copy of the enclosed Form PTO/SB/08, and indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 50-0740 referencing Docket No. 015332.1182-US02.

Dated: February 9, 2016

Respectfully submitted,

By _____

Paul J. Berman
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Melody H. Wu
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PTO/SB/08a (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 8

Complete if Known	
Application Number	Divisional of 14/233,418
Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-7,825,118	11-02-2010	Honigberg et al.	
	AB*	US-7,960,396	06-14-2011	Honigberg et al.	
	AC*	US-8,377,946	02-19-2013	Chen et al.	
	AD*	US-8,658,794	02-25-2014	de Man et al.	
	AE*	US-20060084654-A1	04-20-2006	Beck et al.	
	AF*	US-20080076921-A1	03-27-2008	Honigberg et al.	
	AG*	US-20110257203-A1	10-20-2011	Honigberg et al.	
	AH*	US-20120053189-A1	03-01-2012	Loury	
	AI*	US-20120095026-A1	04-19-2012	Honigberg et al.	
	AJ*	US-20120129821-A1	05-24-2012	Honigberg et al.	
	AK*	US-20120135944-A1	05-31-2012	Honigberg et al.	
	AL*	US-20120165328-A1	06-28-2012	Honigberg et al.	
	AM*	US-20130018032-A1	01-17-2013	Chen et al.	
	AN*	US-20130079327-A1	03-28-2013	Yamamoto et al.	
	AO*	US-20140073593-A1	03-13-2014	Conklin et al.	
	AP*	US-20140206681-A1	07-24-2014	Kim et al.	
	AQ*	US-20140212425-A1	07-31-2014	Chang et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA**	WO-2008121742-A2	10-09-2008	Pharmacyclics, Inc		
	BB**	WO-2010126960-A1	11-04-2010	Locus Pharmaceuticals, Inc		
	BC**	WO-2011095556-A1	08-11-2011	Organon NV		
	BD**	EP-2548877-A1	01-23-2013	MSD Oss B.V.		
	BE**	WO-2001019828-A2	03-22-2001	BASF Aktiengesellschaft		
	BF**	WO-2002080926-A1	10-17-2002	Abbott GmbH & Co. KG		

Examiner Signature		Date Considered	

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DC: 5967927-1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 8

Complete if Known	
Application Number	Divisional of 14/233,418
Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

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	BG**	WO-2003065995-A2	08-14-2003	Supergen, Inc.		
	BH**	WO-2005037836-A2	04-28-2005	OSI Pharmaceuticals, Inc.		
	BI**	WO-2005097800-A1	10-20-2005	OSI Pharmaceuticals, Inc.		
	BJ**	WO-2007061737-A2	05-31-2007	OSI Pharmaceuticals, Inc.		
	BK**	WO-2007064883-A2	06-07-2007	Bayer Pharmaceuticals Corp.		
	BL**	WO-2007064993-A2	06-07-2007	OSI Pharmaceuticals, Inc.		

Examiner Signature		Date Considered	

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Sheet	3	of	8

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First Named Inventor	Tjeerd A. Barf
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	BM**	WO-2007106503-A2	09-20-2007	OSI Pharmaceuticals, Inc.		
	BN**	WO-2009076170-A2	06-18-2009	Novartis AG		
	BO**	WO-2011119663-A1	09-29-2011	Glaxosmithkline LLC		
	BP**	WO-2011152351-A1	12-08-2011	Ono Pharmaceutical Co., Ltd.		
	BQ**	WO-2011153514-A2	12-08-2011	Pharmacyclics, Inc.		
	BR**	WO-2012158843-A2	11-22-2012	Univ. California		

Examiner Signature		Date Considered	

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Sheet 4 of 8

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First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

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	BS**	WO-2013003629-A2	01-03-2013	Pharmacyclics, Inc.		
	BT**	WO-2013010380-A1	01-24-2013	Merck Sharp & Dohme Corp.		
	BU**	WO-2013010868-A1	01-24-2013	MSD Oss B.V.		
	BV**	WO-2013010869-A1	01-24-2013	MSD Oss B.V.		
	BW**	WO-2013059738-A2	04-25-2013	Pharmacyclics, Inc.		
	BX**	WO-2014143807-A2	09-18-2014	Stromatt, Scott		

Examiner Signature		Date Considered	

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Sheet 5 of 8

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First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
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	BY**	WO-2014159745-A1	10-02-2014	Pharmacyclics, Inc.		
	BZ**	WO-2014168975-A1	10-16-2014	Pharmacyclics, Inc.		
	BA1**	WO-2015018522-A1	02-12-2015	Oncoethix SA		

Examiner Signature		Date Considered	

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Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA**	Berge et al., "Pharmaceutical salts," 66(1) J. Pharm. Sci. 1-19 (1977).	
	CB**	Bingham et al., "Over one hundred solvates of sulfathiazole," Chem. Commun. 603-04 (2001).	
	CC**	Caira et al., "Preparation and Crystal Characterization of a Polymorph, a Monohydrate, and an Ethyl Acetate Solvate of the Antifungal Fluconazole," 93(3) J. Pharma. Sci. 601-11 (2004).	
	CD**	Davis et al., "Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma," 463 Nature 88-92 (2010).	
	CE**	Dhar et al., "Synthesis and SAR of p38α MAP kinase inhibitors based on heterobicyclic scaffolds," 17 Bioorg. & Med. Chem. Lett. 5019-24 (2007).	
	CF**	Gaudet et al., "A Homogeneous Fluorescence Polarization Assay Adaptable for a Range of Protein Serine/Threonine and Tyrosine Kinases," 8(2) J. Biomol. Screening 164-75 (2003).	
	CG**	Gennaro (ed.), *Remington: The Science and Practice of Pharmacy*, 20th edition (2000).	
	CH**	Gilfillan et al., "The tyrosine kinase network regulating mast cell activation," 288 Immun. Rev. 149-69 (2009).	
	CI**	Gould, "Salt selection for basic drugs," 33 Int'l J. Pharmaceutics 201-217 (1986).	
	CJ**	Greene & Wuts, *Protective Groups in Organic Synthesis*, 2d Edition (1991).	

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CK**	Harder et al., "Gain- and Loss-of-Function Lyn Mutant Mice Define a Critical Inhibitory Role for Lyn in the Myeloid Lineage," 15 Immunity 603-15 (2001).	
	CL**	Hartz et al., "Synthesis and Evaluation of Imidazo[1,5-α]pyrazines as Corticotropin Releasing Hormone Receptor Ligands," 12 Bioorg. & Med. Chem. Lett. 291-94 (2002).	
	CM**	Higuchi *et al.* (eds.), *Pro-drugs as Novel Delivery Systems,* 14 A.C.S. Symposium Series (1975).	
	CN**	Ji et al., "A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling *in vitro* and inhibits insulin-like growth factor-I receptor-dependent tumor growth *in vivo*," 6(8) Mol. Cancer Ther. 2158-67 (2007).	
	CO**	King et al., "Nucleofugality effects in the pyridine promoted formation of esters from 2-substituted ethanesulfonyl chlorides," 66 Can. J. Chem. 1109-16 (1988).	
	CP**	Klinghoffer et al., "Src family kinases are required for integrin but not PDGFR signal transduction," 18(9) EMBO J. 2459-71 (1999).	
	CQ**	Lim et al., "Anti-CD20 monoclonal antibodies: historical and future perspectives," 95(1) Haematologica 135-43 (2010).	
	CR**	Lowell et al., "Deficiency of the Hck and Src Tyrosine Kinases Results in Extreme Levels of Extramedullary Hematopoiesis," 87(5) Blood 1780-92 (1996).	
	CS**	Mitchell et al., Synthesis of *C*-nucleoside isosteres of 9-(2-hydroxyethoxymethyl)guanine (acyclovir)," 21(3) J. Heterocyclic Chem. 697-99 (1984).	
	CT**	Mukaiyama et al., "Synthesis and c-Src inhibitory activity of imidazo[1,5-α]pyrazine derivatives as an agent for treatment of acute ischemic stroke," 15 Bioorg. & Med. Chem. 868-85 (2007).	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ** CITE NO.: Those document(s) which are marked with an double asterisk (**) next to the Cite No. are not supplied because they were previously cited by or submitted to the Office in a prior application relied upon in this application for an earlier filing date under 35 U.S.C. 120.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	8	of	8

Complete if Known	
Application Number	Divisional of 14/233,418
Filing Date	February 9, 2016
First Named Inventor	Tjeerd A. Barf
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	015332.1182-US02

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CU**	Mulvihill et al., "1,3-Disubstituted-imidazo[1,5-α]pyrazines as insulin-like growth-factor-I receptor (IGF-IR) inhibitors," 17 Bioorg. & Med. Chem. Lett. 1091-97 (2007).	
	CV**	Mulvihill et al., "Novel 2-phenylquinolin-7-yl-derived imidazo[1,5-α]pyrazines as potent insulin-growth factor-I receptor (IGF-IR) inhibitors," 16 Bioorg. & Med. Chem. 1359-75 (2008).	
	CW**	Odom et al., "Negative Regulation of Immunoglobulin E-dependent Allergic Responses by Lyn Kinase," 199(11) J. Exp. Med. 1491-1502 (2004).	
	CX**	Pan et al., "Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase," 2 ChemMedChem 58-61 (2007).	
	CY**	Roby et al., "Alterations in Reproductive Function in Src Tyrosine Kinase Knockout Mice," 26 Endocrine 169-76 (2005).	
	CZ**	Roche (ed.), *Bioreversible Carriers in Drug Design*, Pergamon Press (1987).	
	CA1**	Shinohara et al., "Tyrosine Kinases Btk and Tec Regulate Osteoclast Differentiation by Linking RANK and ITAM Signals," 132 Cell 794-806 (2008).	
	CB1**	van Tonder et al., "Preparation and Physicochemical Characterization of 5 Niclosamide Solvates and 1 Hemisolvate," 5(1) AAPS PharmSciTech Article 12 (2004).	

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Filer:	Andrea Reister/Jenn Augsburger
Attorney Docket Number:	015332.1182-US02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1740

Electronic Acknowledgement Receipt	
EFS ID:	24868413
Application Number:	15019543
International Application Number:	
Confirmation Number:	1984
Title of Invention:	4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS
First Named Inventor/Applicant Name:	Tjeerd A. Barf
Customer Number:	26853
Filer:	Andrea Reister/Jenn Augsburger
Filer Authorized By:	Andrea Reister
Attorney Docket Number:	015332.1182-US02
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		14233418-DivisionalApplication-ADS-IDS.pdf	1786233 ebaafcccba346b7025ed07bcae055ad45bd3f0ad	yes	134

Multipart Description/PDF files in .zip description

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2	Fee Worksheet (SB06)	fee-info.pdf	37002 6fde58fc75ea81474fc6a2686e3b975f80178cd4	no	2

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 015332.1182-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tjeerd A. Barf et al.

Application No.: Divisional of 14/233,418 | Confirmation No.: Not Yet Assigned

Filed: February 9, 2016 | Art Unit: Not Yet Assigned

For: 4-IMIDAZOPYRIDAZIN-1-YL-BENZAMIDES AND 4-IMIDAZOTRIAZIN-1-YL-BENZAMIDES AS BTK INHIBITORS | Examiner: Not Yet Assigned

TRANSMITTAL LETTER

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

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Utility Patent Application Transmittal;

2. Utility application comprising: ninety-seven (97) pages of description; eleven (11) pages of claims; and one (1) page abstract;

3. Application Data Sheet; and

4. Information Disclosure Statement with Form PTO/SB/08.

This application is being filed as a divisional of U.S. Patent Application No. 14/233,418 due to the restriction requirement concerning that application as set forth in the Office Action dated

November 10, 2014 (Paper No. 20141104-2169 for US 14/233,418) and as further clarified and confirmed by the Examiner of US 14/233,418 by telephone discussions on August 13, 2015, and August 27, 2015. Please see the Amendment in Response to Non-Final Office Action Under 37 C.F.R. § 1.111, filed in US 14/233,418 on September 25, 2015, for a detailed discussion of the restriction and election requirements in US 14/233,418.

In response to the restriction requirement in Application No. 14/233,418, Applicant elected the claims of Group I, drawn to a compound of Formula (I). The Examiner made clear that any method claims, including claims to methods of treatment, could not be presented in US 14/233,418 and would have to be presented in one or more divisional applications. As such, method claims 1-11 are presented in the subject divisional application.

Original claim 16 of Application No. 14/233,418 recited "A combination of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a further therapeutic agent." Claim 16 was grouped by the Examiner into non-elected Group II, and Applicant cancelled this claim (and others) in a manner consonant with the finality of the restriction requirement. Applicant now presents combination claims 12-18 in the subject divisional application.

Please charge our Deposit Account No. 50-0740 in the amount of $1,740 in payment of the following fees: basic filing fee - utility ($280); utility search fee ($600); utility examination fee ($720); and surcharge for late filing of declaration ($140). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or that should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0740, under Docket No. 015332.1182-US02.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor

(including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: February 9, 2016

Respectfully submitted,

By _____

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