

PYRIMIDINE-BASED BICYCLES AS ANTIVIRAL AGENTS FOR THE TREATMENT AND PREVENTION OF HIV INFECTION

Description

Technical Field

This invention relates to pyrimidine derivatives, having HIV replication inhibiting. The present invention provides new pyrimidine compounds of formula I. The compounds can be used for the treatment and/or prevention of HIV-mediated diseases. The invention further relates to methods of obtaining said compounds and pharmaceutical compositions contained thereof. The invention also relates to the use of abovementioned compounds for the treatment and/or prevention of HIV in subjects with HIV-infection (human immunodeficiency virus) or having risk of getting HIV-infection.

Background Art

Compounds structurally related to the present antiviral compounds are disclosed
15 in the prior art:

References:

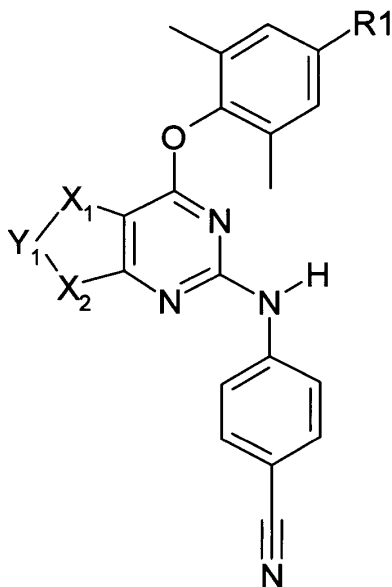
20 J. Guillemont et al., application WO 2006/035068, published on April 6, 2006,
J. Guillemont et al., application WO 2006/035067, published on April 6, 2006,
J. Guillemont et al., application WO 2006/045828, published on May 4, 2006,
J. Guillemont et al., application WO 2006/035369, published on April 6, 2006,
H.A. De Koek and P. Wigerinck, application WO 2006/094930, published on
September 14, 2006.

H.A. De Koek and P. Wigerinck, application WO 2006/087387, published on August 24, 2006.

25 P.A.J. Jansen et al., *J. Med. Chem.*, 48(6), 1901-1909 (2005)
K. Das et al., *J. Med. Chem.*, 47(10), 2550-2660 (2004).
J. Guillemont et al., *J. Med. Chem.*, 48(6), 2072-2079 (2005).

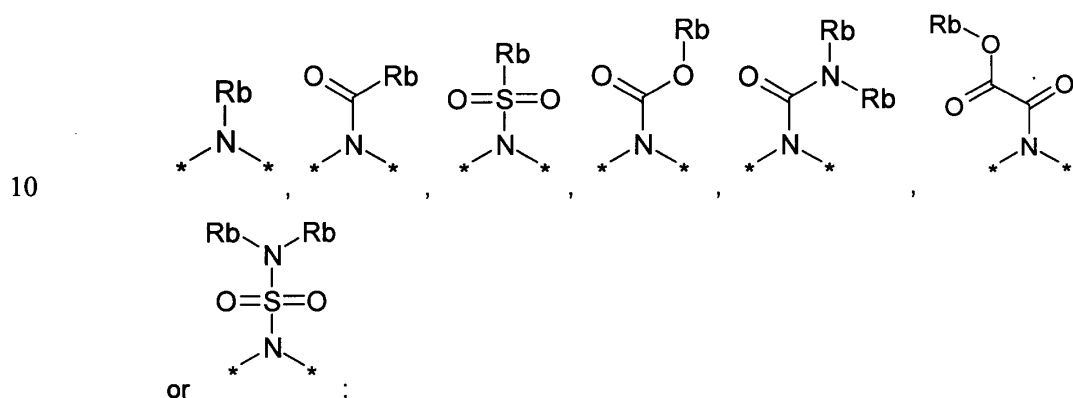
Disclosure of Invention

This invention concerns to the compound of formula I



(I)

- 5 , where **R¹** is independently selected and represents H-, -CN, CN-CH=CH-;
X¹, **X²** is a substituent of (CH₂)_n type, wherein n is independently selected for **X₁**,
X₂ and may have values of between 1 and 3;
Y¹ is independently selected and represents -O-, -S-, -S(=O)-, -S(=O)₂-, or
substituents of the following type:



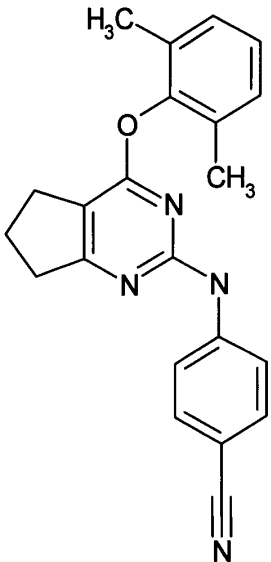
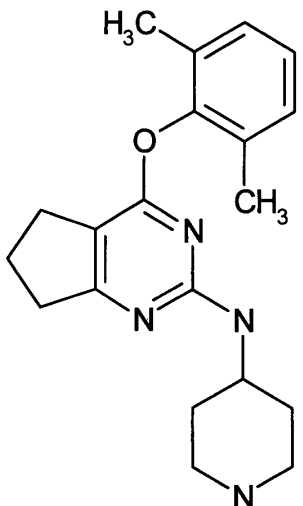
- 15 **R^b** is independently selected and represents -H, substituted or unsubstituted -C₁-C₆-alkyl, substituted or unsubstituted -C₁-C₆-alkenyl, substituted or unsubstituted -C₆-aryl, substituted or unsubstituted -5-6-membered-heteroaryl containing 1 to 4 heteroatoms independently selected from N, S and/or O, substituted or unsubstituted -C₃-C₉-cycloalkyl, or substituted or unsubstituted 4-9-membered heterocyclyl containing 1 to 4 heteroatoms independently selected from N, S and/or O; or pharmaceutically

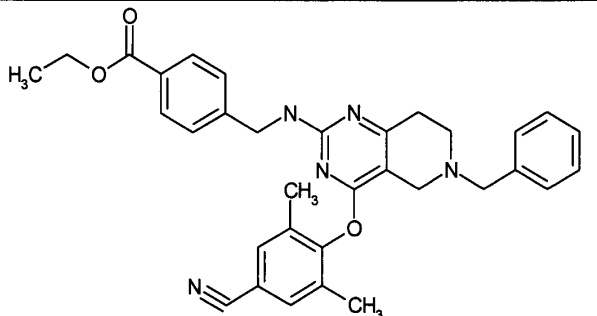
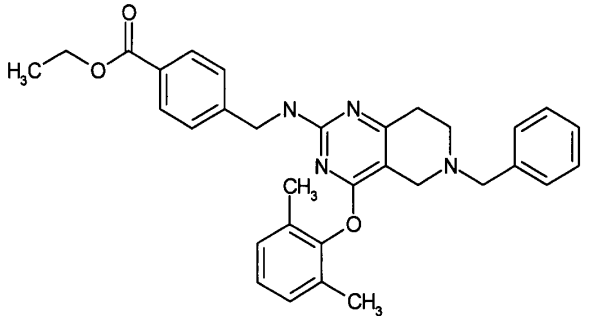
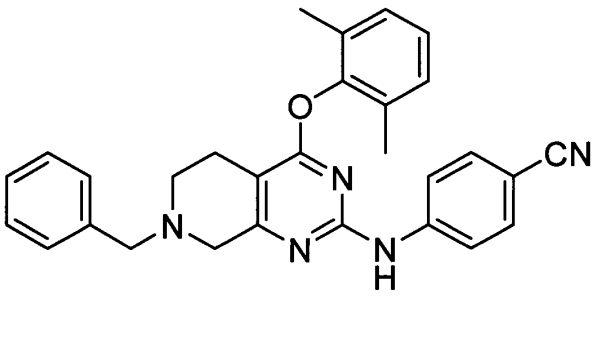
acceptable salts thereof.

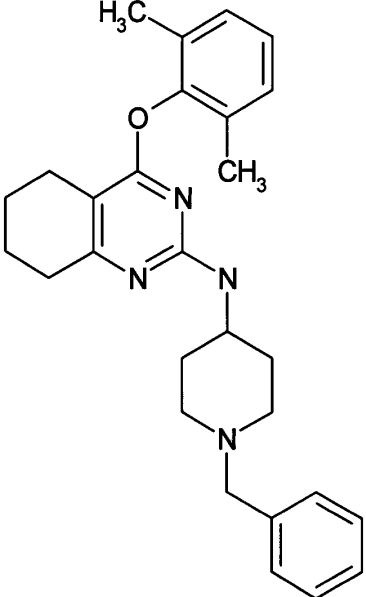
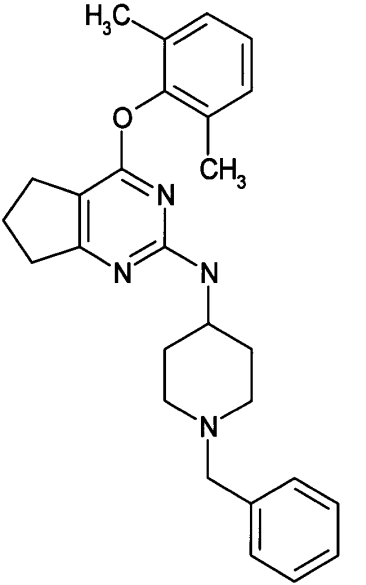
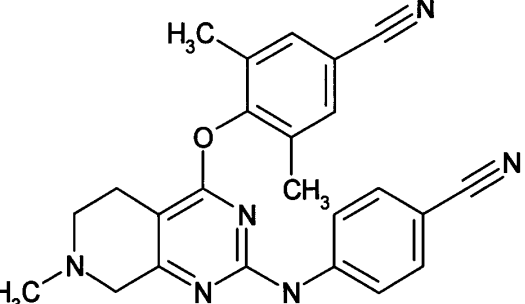
Compounds of formula I inhibit HIV-1 reverse transcriptase and can be used in the method for the treatment and/or prevention of HIV-mediated diseases.

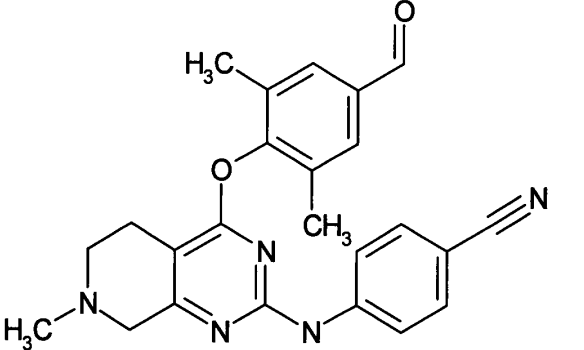
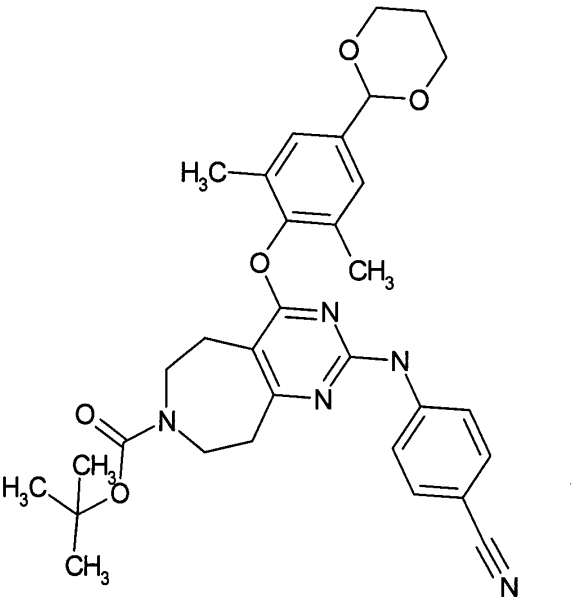
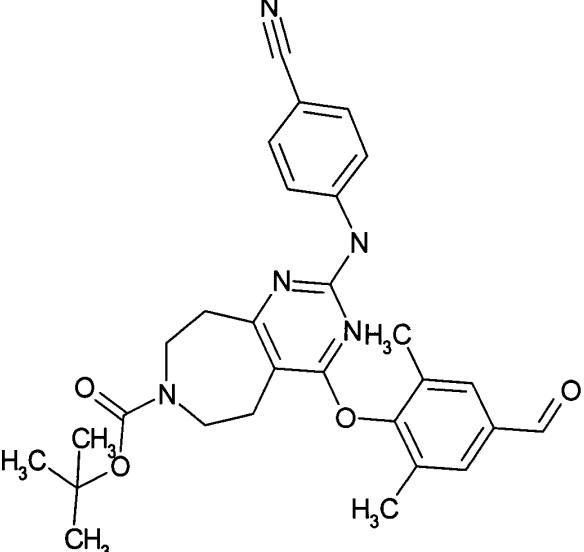
The present invention further relates to the composition, containing compounds of formula I, which can be used for the treatment and/or prevention of HIV-mediated diseases. This invention also relates to compounds of formula I, which can be used for the treatment as a single therapeutic agent or in combination with other antiviral agents.

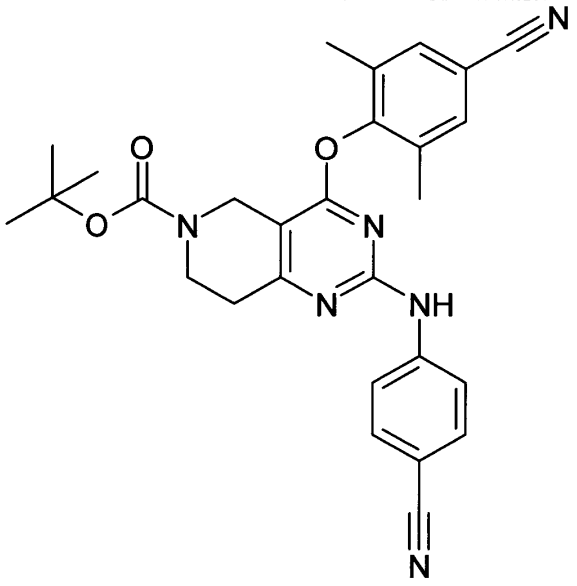
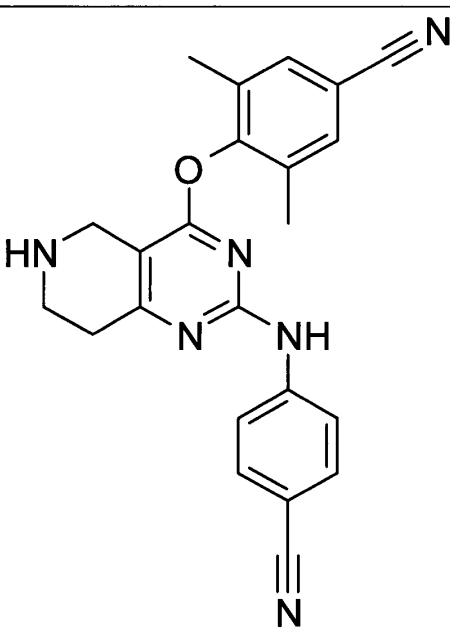
In one embodiment, the present invention relates to one of the following compounds:

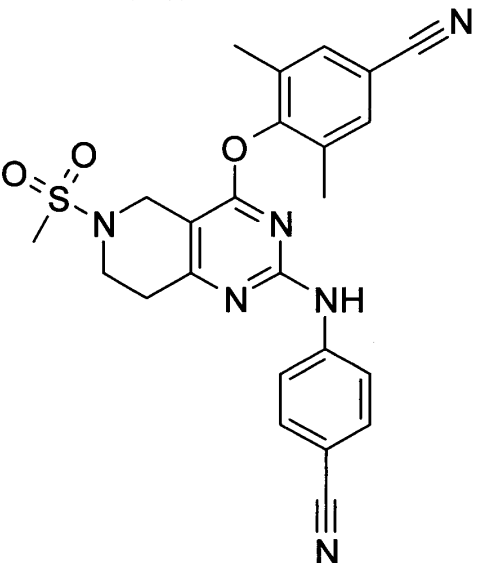
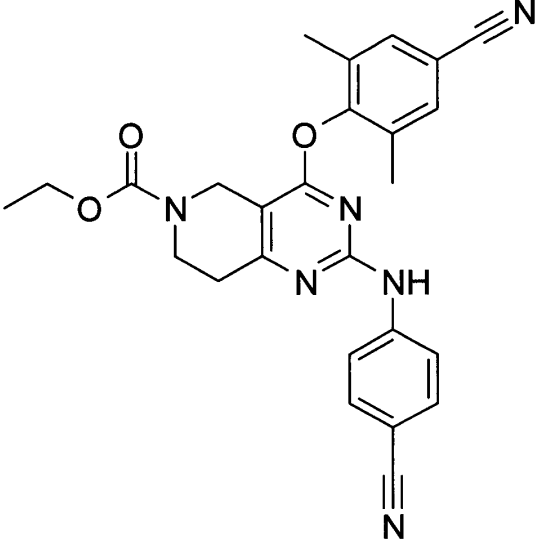
	Structural formula	Name
0272161		4-((4-(2,6-Dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-yl)amino)benzonitrile
0272208		4-(2,6-Dimethylphenoxy)-N-(piperidine-4-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine

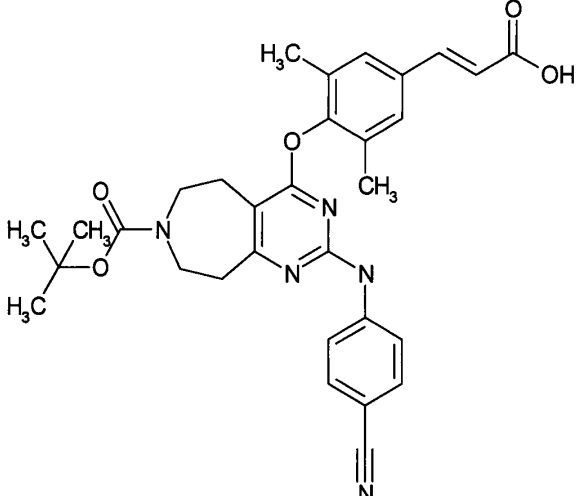
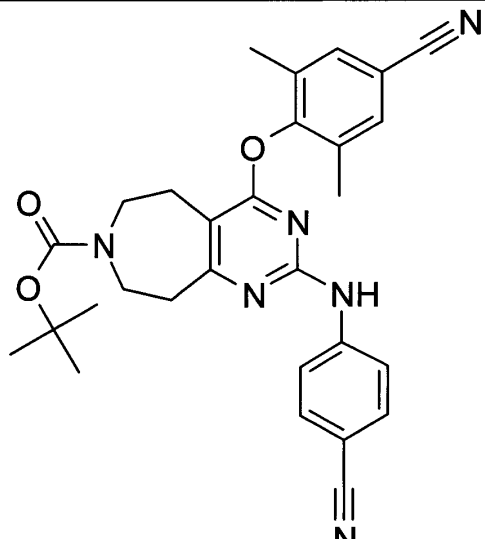
0273457		Ethylic ether 4-(((6-benzyl-4-(4-cyano-2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid
0273458		Ethylic ether 4-(((6-benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid
0273459		4-(((7-Benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)methyl)benzonitrile

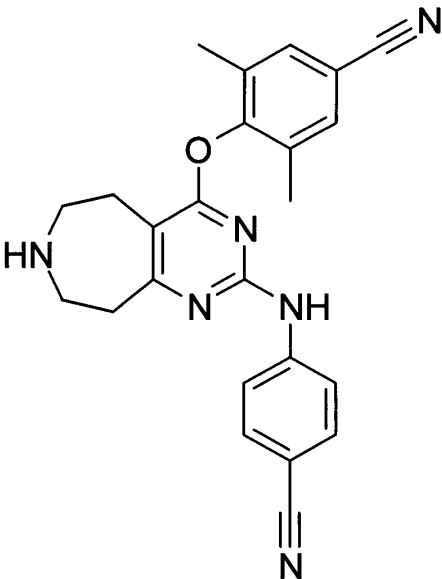
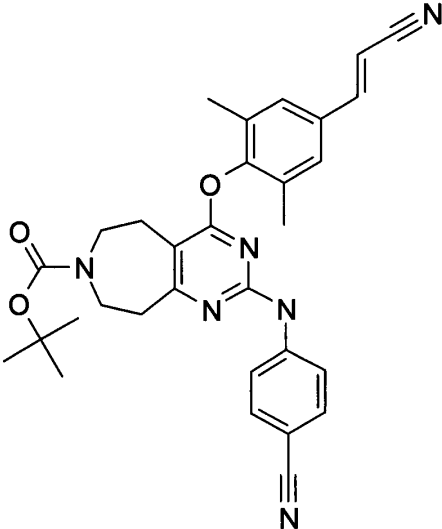
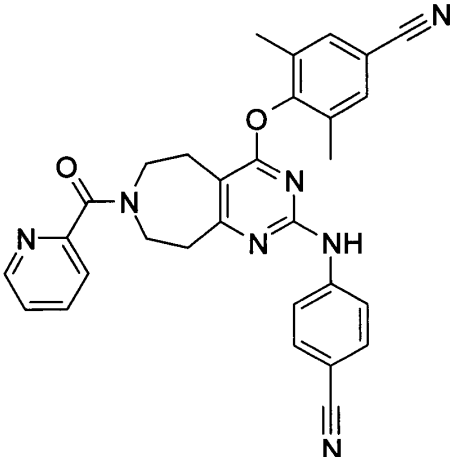
0273460		N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydroquinazoline-2-amine
0273461		N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine
0273774		4-((2-((4-cyanophenyl)amino)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile

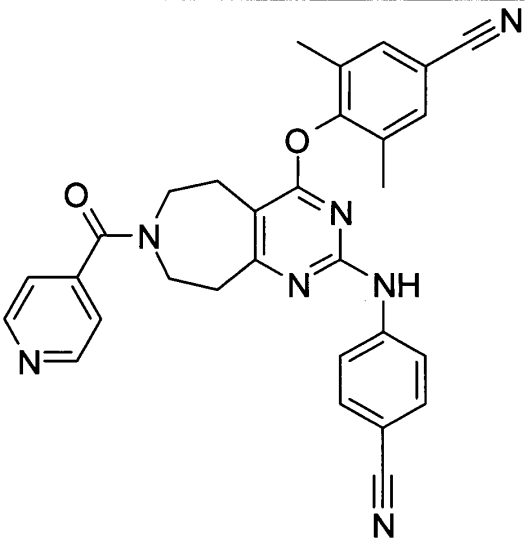
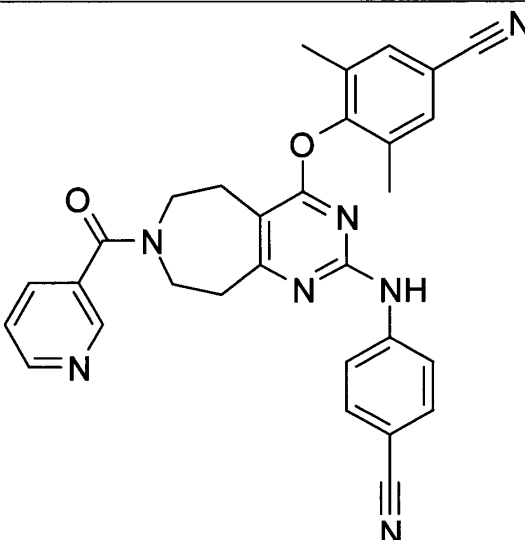
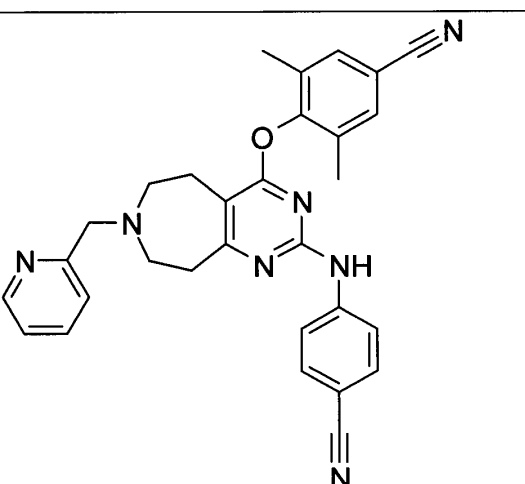
0273775		4-((4-(4-Formyl-2,6-dimethylphenoxy)-7-methyl-5,6,7,8-tetrahydro[3,4-d]pyrimidine-2-yl)amino)benzonitrile
0273892		Tert-butyl 4-(4-(1,3-dioxolane-2-yl)-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate
0273943		Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-formyl-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

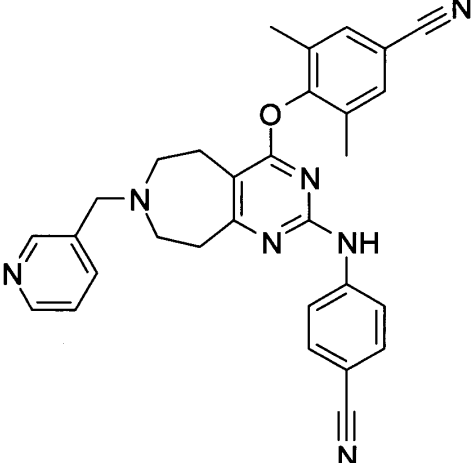
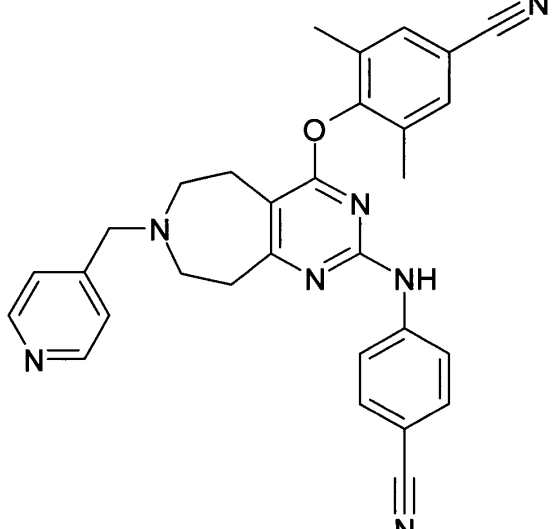
0273961		Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate
0273963		4-((2-((4-Cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

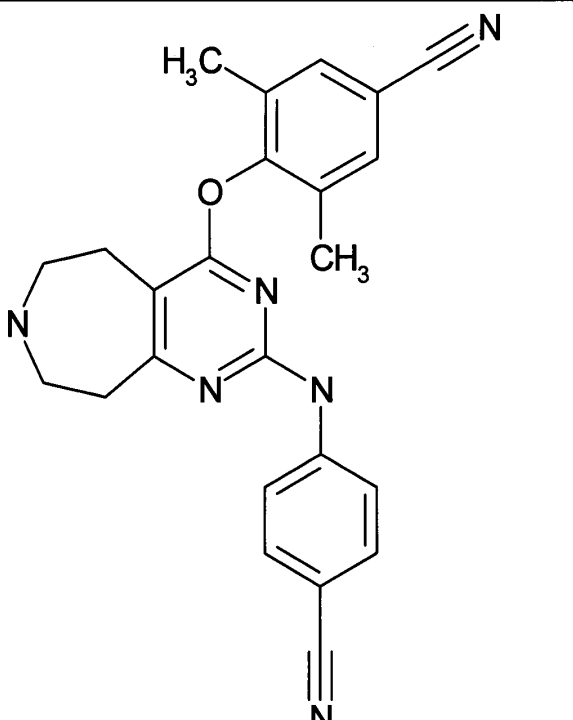
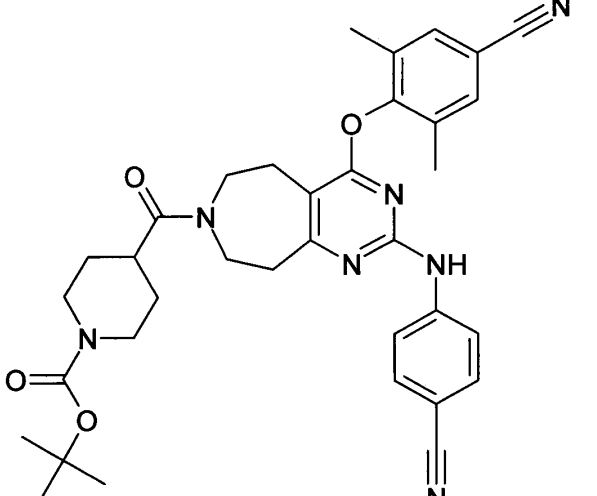
0273964	 The structure shows a 4-cyanophenyl group connected via an amino group to the 2-position of a 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine ring. The 6-position of this ring is substituted with a methylsulfonyl group. The 4-position of the pyrimidine ring is connected via an oxygen atom to a 2,6-dimethyl-4-cyanophenyl group.	4-((2-((4-Cyanophenyl)amino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile
0273965	 The structure shows a 4-cyanophenyl group connected via an amino group to the 2-position of a 7,8-dihydropyrido[4,3-d]pyrimidine ring. The 6-position of this ring is substituted with an ethyl ester group. The 4-position of the pyrimidine ring is connected via an oxygen atom to a 2,6-dimethyl-4-cyanophenyl group.	Ethyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

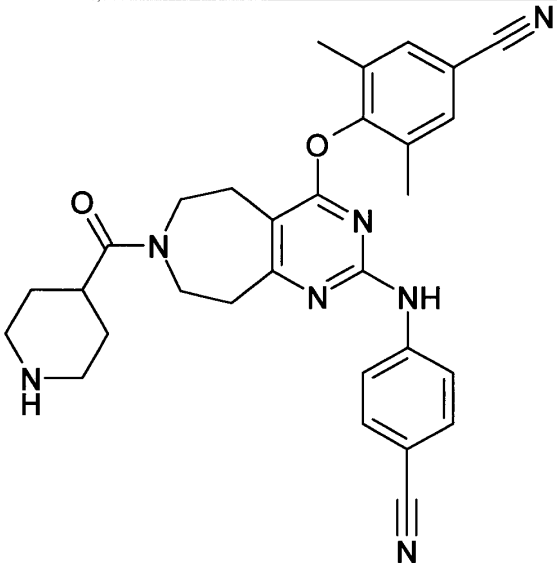
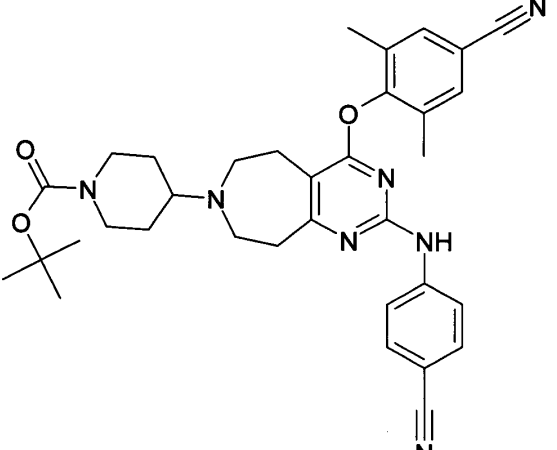
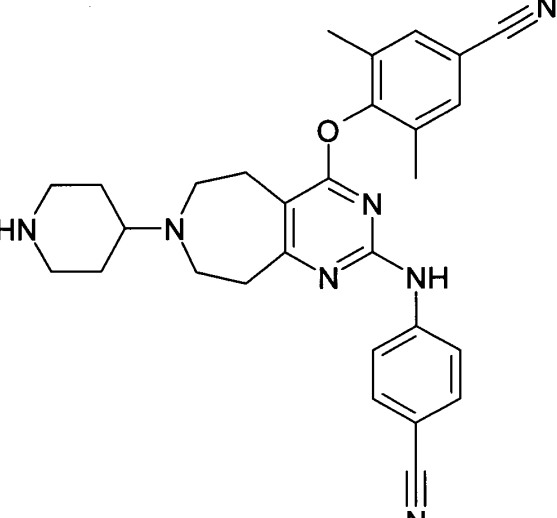
0273969		(E)-3-(4-((7-(Tert-butoxycarbonyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylphenyl)acrylic acid
0273972		Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

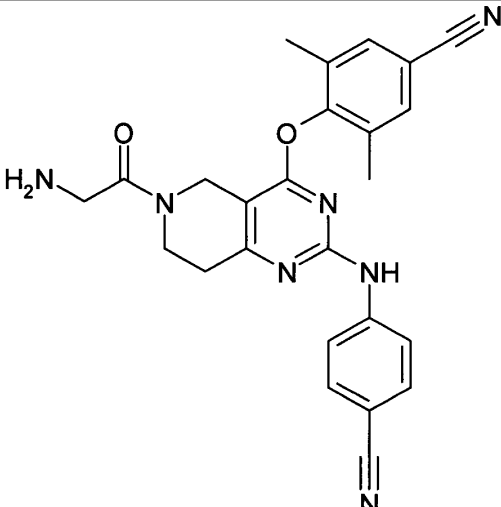
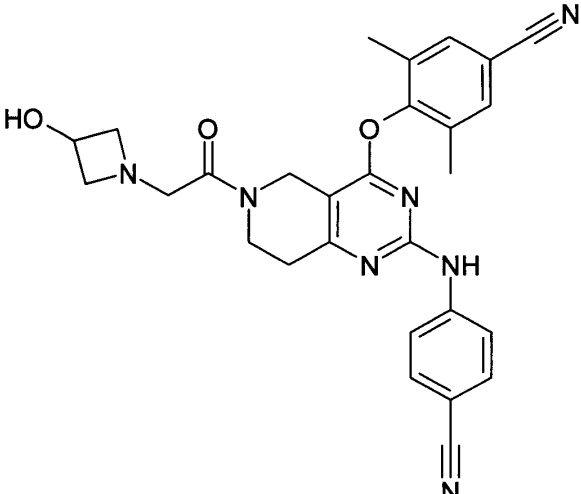
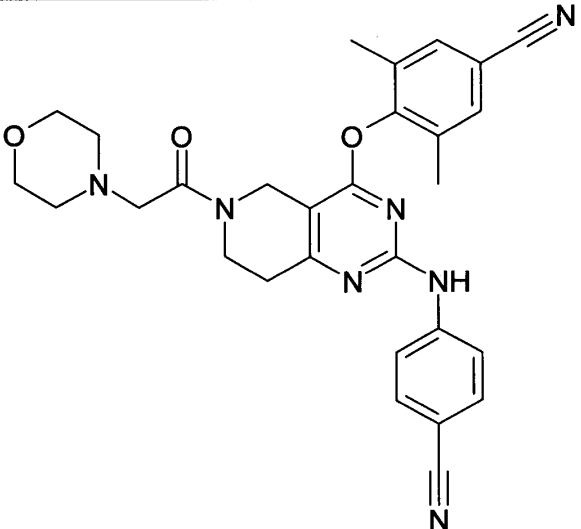
0273976		4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274009		Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-(2-cyanovinyl)-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate
0274010		4-((2-((4-Cyanophenyl)amino)-7-picolynoyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

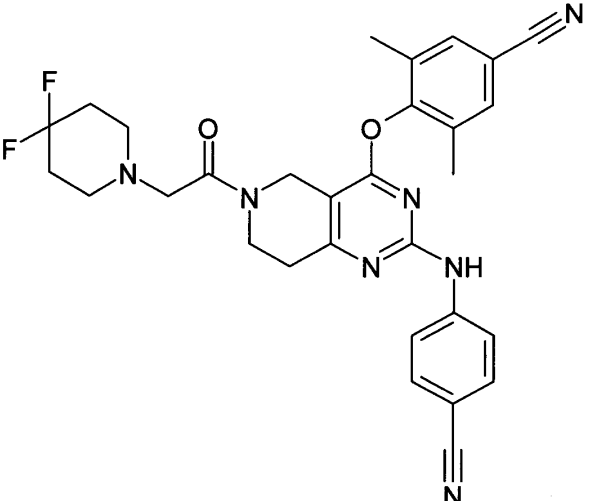
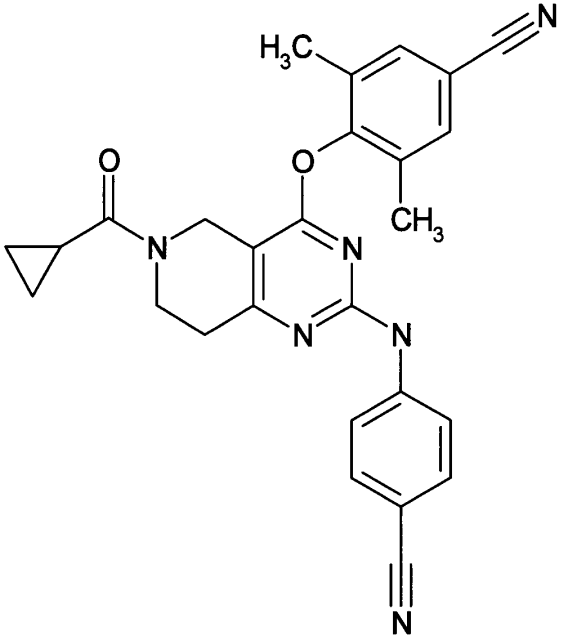
0274011		4-((2-((4-Cyanophenyl)amino)-7-isonicotinoyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274012		4-((2-((4-Cyanophenyl)amino)-7-nicotinoyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274014		4-((2-((4-Cyanophenyl)amino)-7-(pyridine-2-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

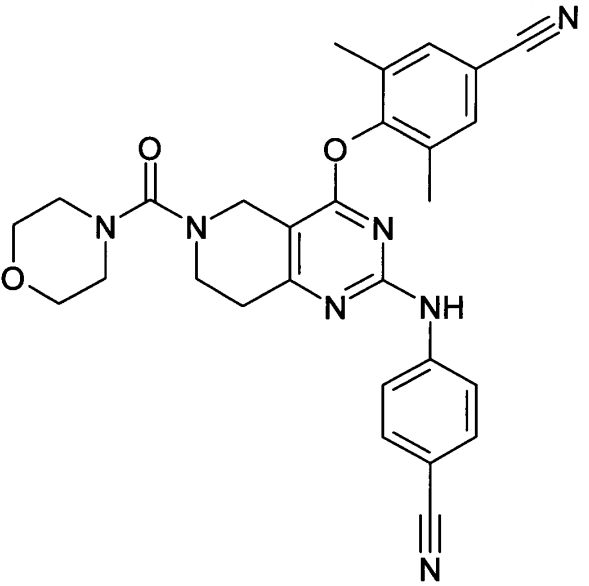
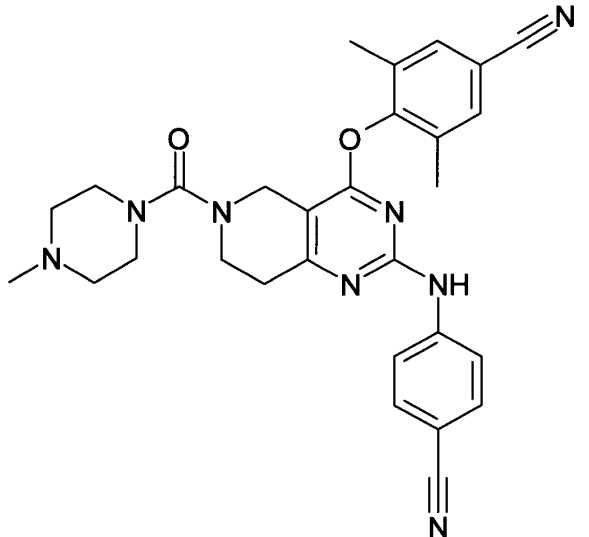
0274015	 The chemical structure shows a 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine core. At position 2, there is a 4-cyanophenylamino group. At position 7, there is a pyridine-3-ylmethyl group. At position 4, there is an oxygen atom connected to a 3,5-dimethyl-4-cyanophenyl group.	4-((2-((4-Cyanophenyl)amino)-7-(pyridine-3-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274016	 The chemical structure is similar to the one above, but the pyridine ring is substituted at the 4-position instead of the 3-position.	4-((2-((4-Cyanophenyl)amino)-7-(pyridine-4-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

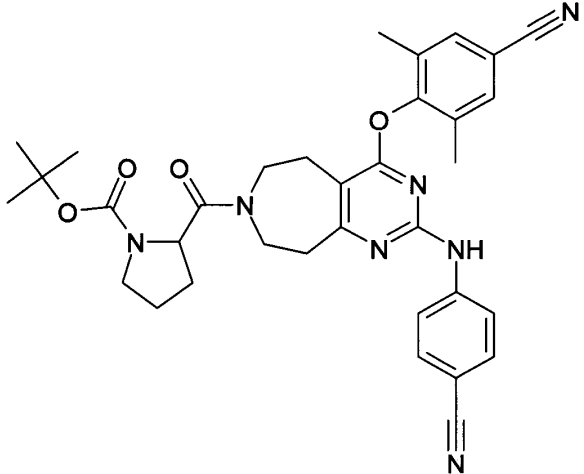
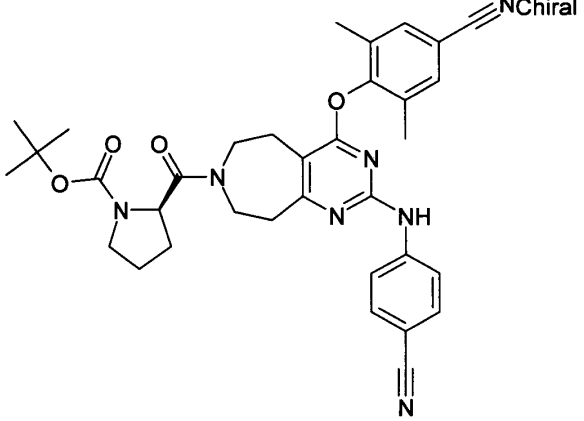
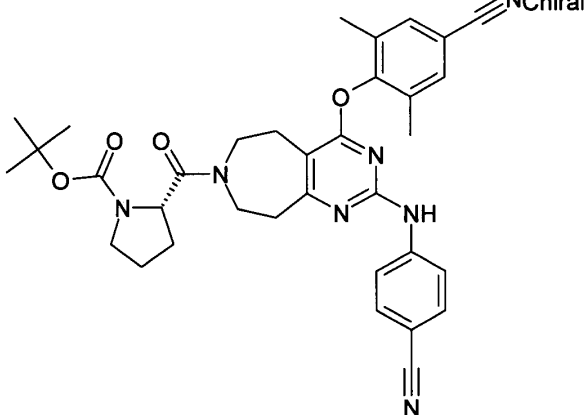
0274021	 The structure shows a 3,5-dimethylbenzonitrile moiety connected via an ether oxygen to the 2-position of a 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine ring. The 4-position of the pyrimidine ring is substituted with a 4-cyanophenyl group.	4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274025	 The structure features a 4-cyano-2,6-dimethylphenoxy group attached to the 2-position of a 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine ring. The 4-position of the pyrimidine ring is substituted with a 4-cyanophenyl group. The 7-position of the azepine ring is linked via a carbonyl group to a piperidine ring, which is further substituted with a tert-butyl ester group.	Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]asein-7-carbonyl)piperidine-1-carboxylate

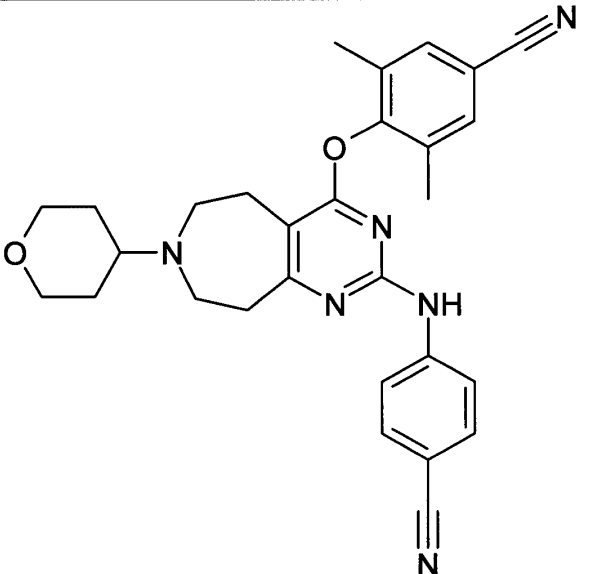
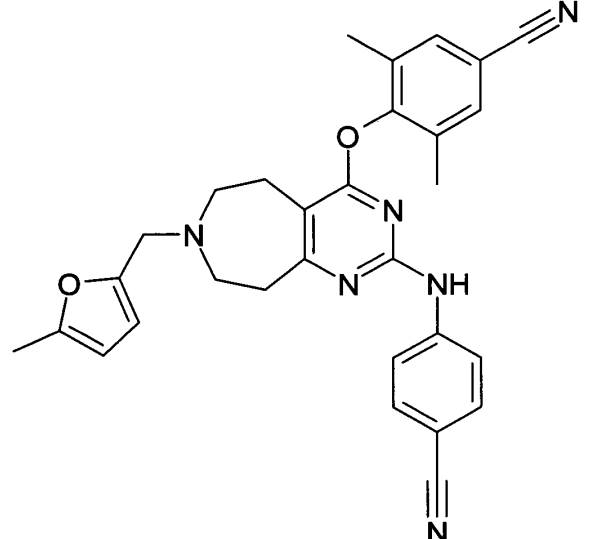
0274026		4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274027		Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)piperidine-1-carboxylate
0274028		4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

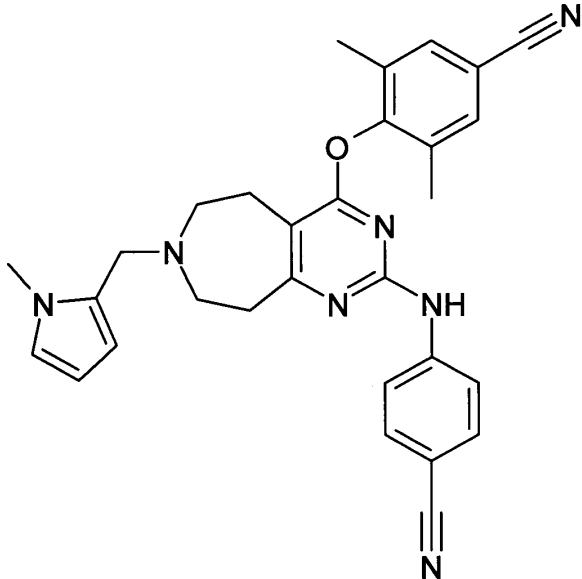
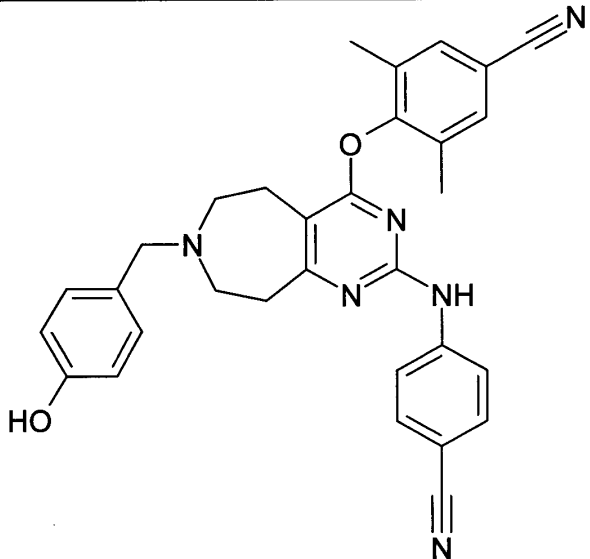
0274051		4-((6-(2-Aminoacetyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274052		4-((2-((4-Cyanophenyl)amino)-6-(2-(3-hydroxyazetidine-1-yl)acetyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274053		4-((2-((4-Cyanophenyl)amino)-6-[2-(morpholine-4-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

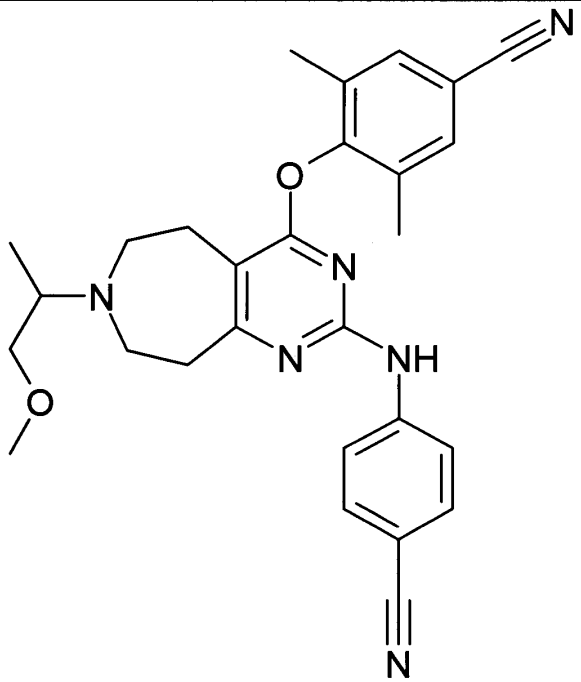
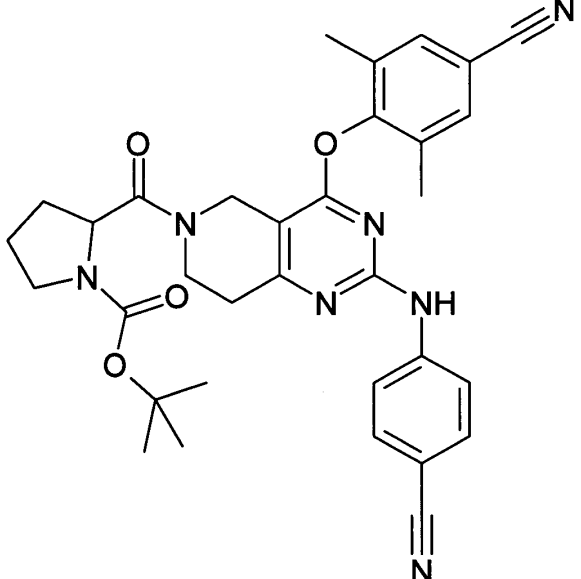
0274054		4-((2-((4-Cyanophenyl)amino)-6-[2-(4,4-difluoropiperidine-1-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274055		4-((2-((4-Cyanophenyl)amino)-7-(cyclopropanecarbonyl)-5,6,7,8-tetrahydro-[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

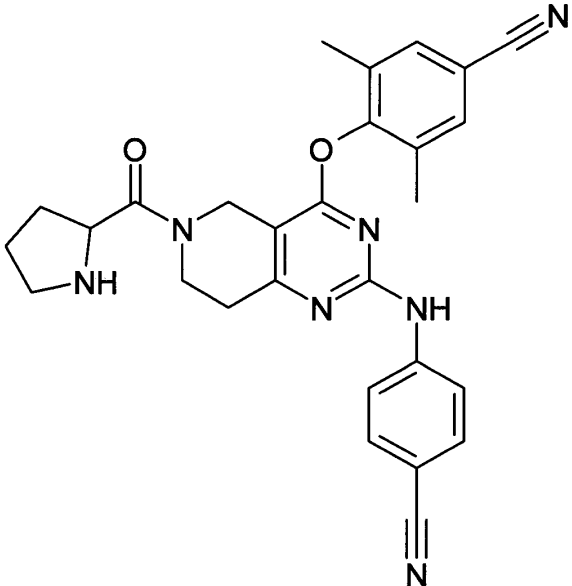
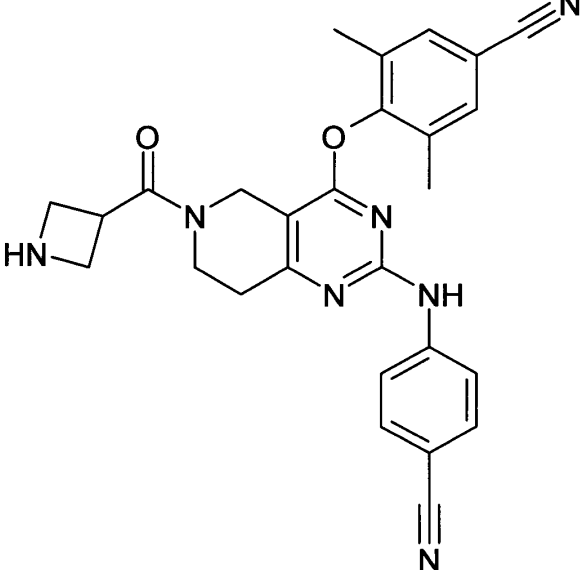
0274056	 The chemical structure shows a central pyrido[4,3-d]pyrimidine core. At the 2-position, there is an amino group (-NH-) linked to a 4-cyanophenyl ring. At the 6-position, there is an oxygen atom linked to a 3,5-dimethylbenzonitrile ring. At the 4-position, there is a carbonyl group (-C(=O)-) linked to a morpholine ring.	4-((2-[(4-Cyanophenyl)amino]-6-(morpholine-4-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274057	 The chemical structure is similar to the one above, but the morpholine ring is replaced by a 4-methylpiperazine ring, which has a methyl group attached to one of its nitrogen atoms.	4-((2-[(4-Cyanophenyl)amino]-6-(4-methylpiperazine-1-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

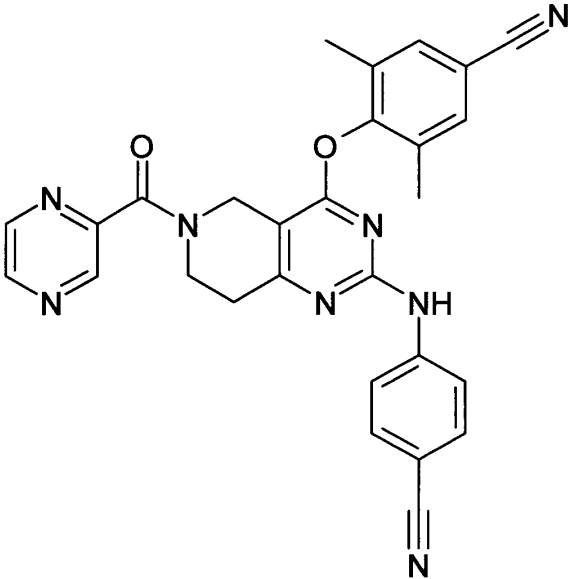
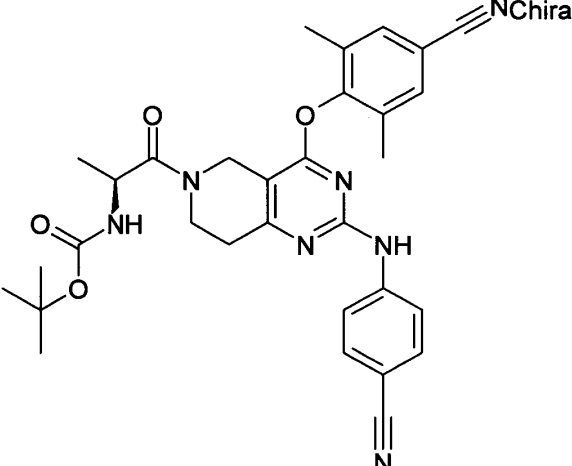
0274063		Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate
0274064		(R)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate
0274065		(S)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate

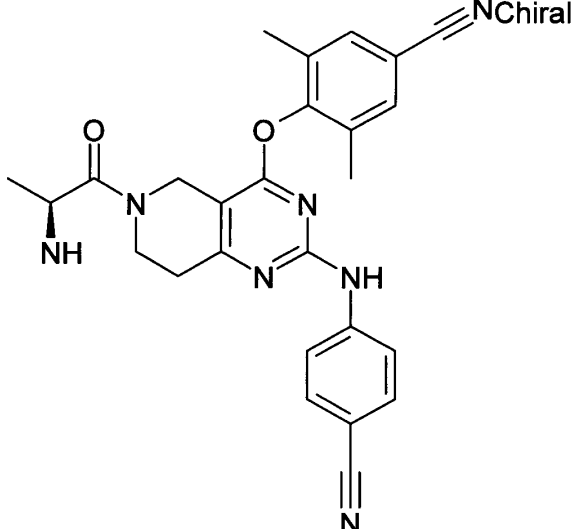
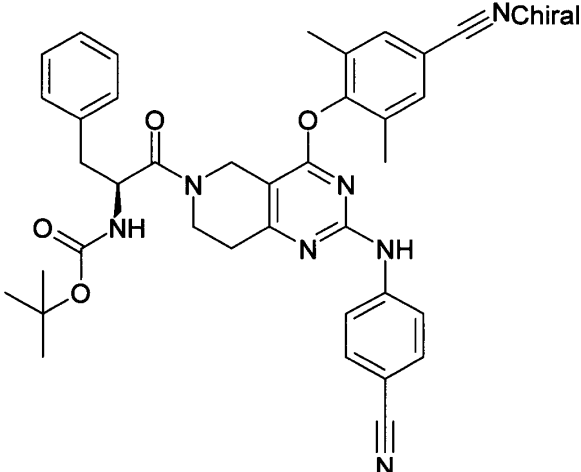
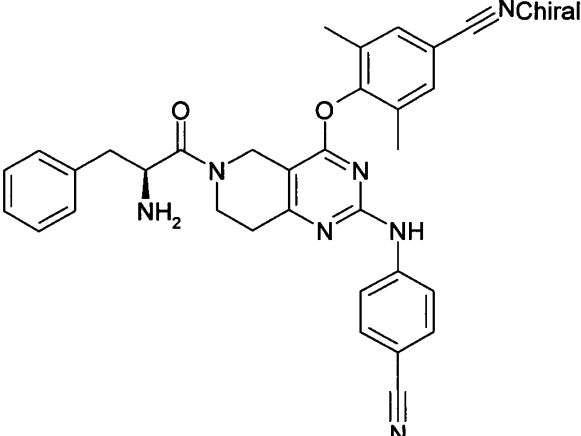
0274072		4-((2-((4-Cyanophenyl)amino)-7-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274073		4-((2-((4-Cyanophenyl)amino)-7-(5-methylfuran-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

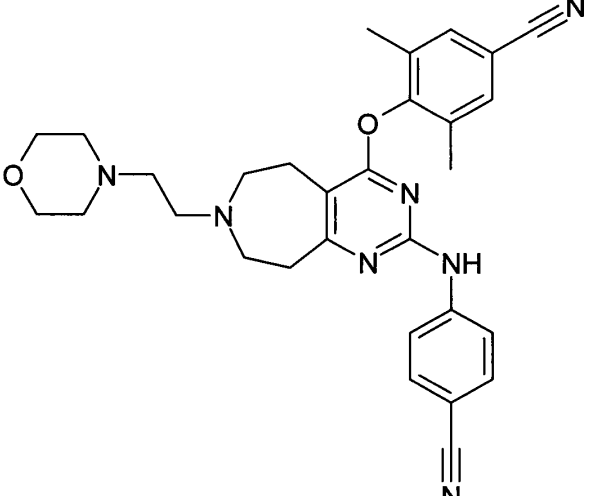
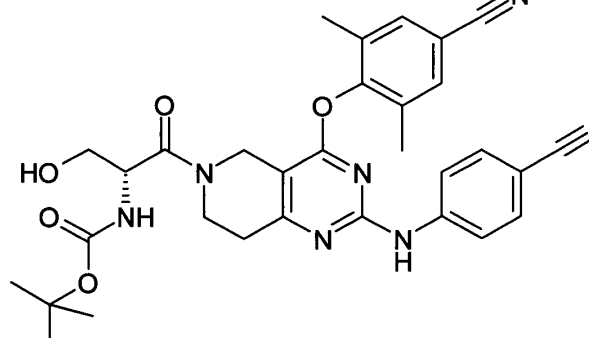
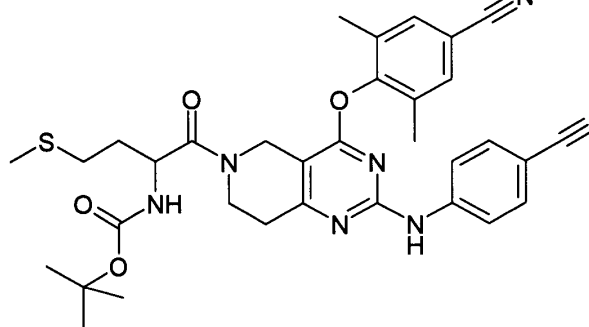
0274074		4-((2-((4-Cyanophenyl)amino)-7-(1-methyl-1H-pyrrol-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274075		4-((2-((4-Cyanophenyl)amino)-7-(4-hydroxybenzyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

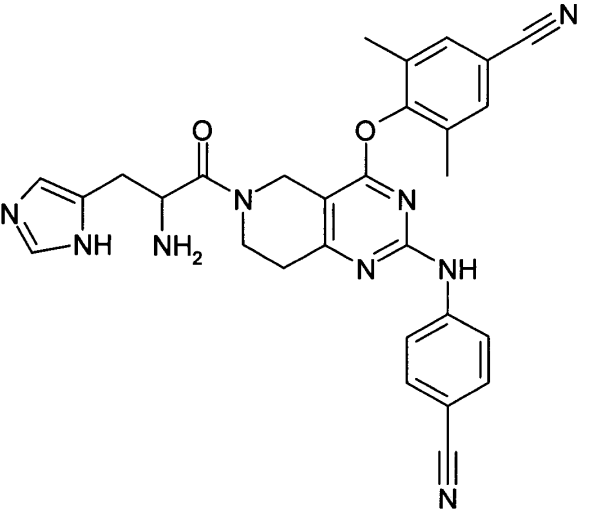
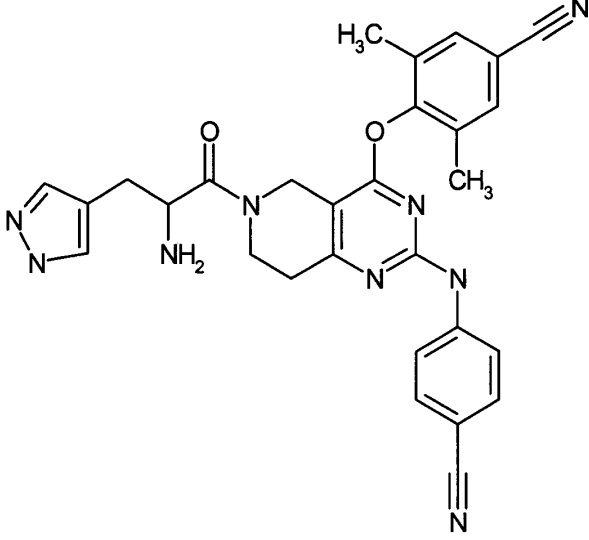
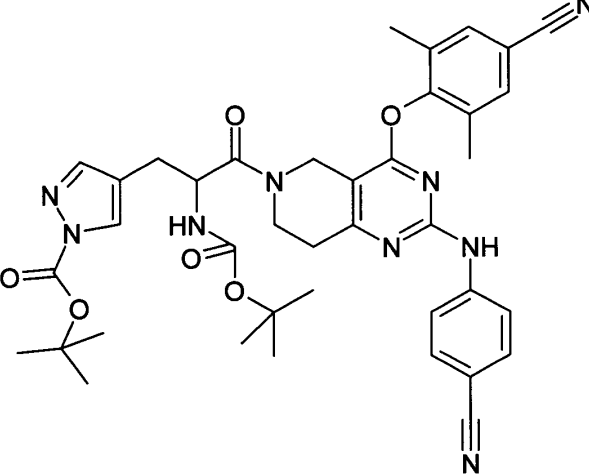
0274080		4-((2-((4-Cyanophenyl)amino)-7-(1-methoxypropane-2-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274097		Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-6-carbonyl)pyrrolidine-1-carboxylate

0274098	 The chemical structure shows a central pyrimidine ring fused to a tetrahydropyridine ring. The pyrimidine ring has an amino group at position 2, which is connected to a 4-cyanophenyl group. The tetrahydropyridine ring has a carbonyl group at position 6, which is connected to a pyrrolidine ring. The pyrimidine ring also has an oxygen atom at position 4, which is connected to a 3,5-dimethyl-4-cyanophenyl group.	4-((2-((4-Cyanophenyl)amino)-6-(pyrrolidine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274099	 The chemical structure is similar to the one in the first row, but the pyrrolidine ring is replaced by an azetidine ring. The central pyrimidine ring is fused to a tetrahydropyridine ring. The pyrimidine ring has an amino group at position 2, which is connected to a 4-cyanophenyl group. The tetrahydropyridine ring has a carbonyl group at position 6, which is connected to an azetidine ring. The pyrimidine ring also has an oxygen atom at position 4, which is connected to a 3,5-dimethyl-4-cyanophenyl group.	4-((6-(Azetidine-3-carbonyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

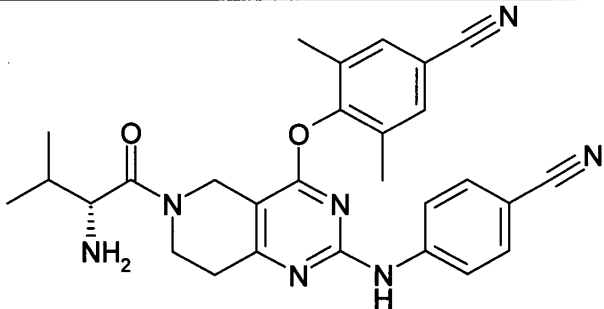
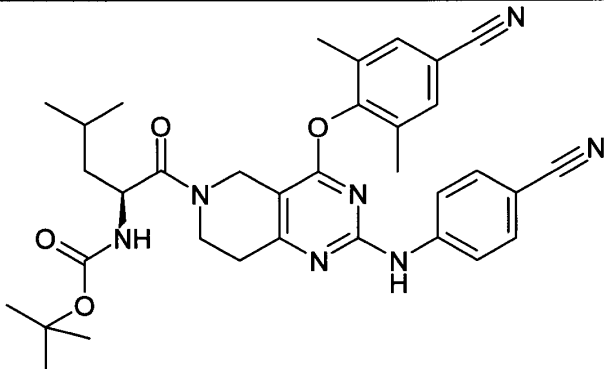
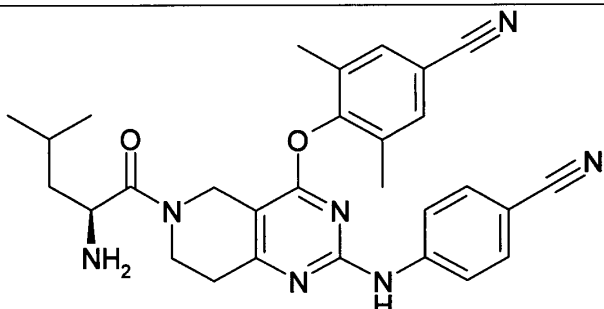
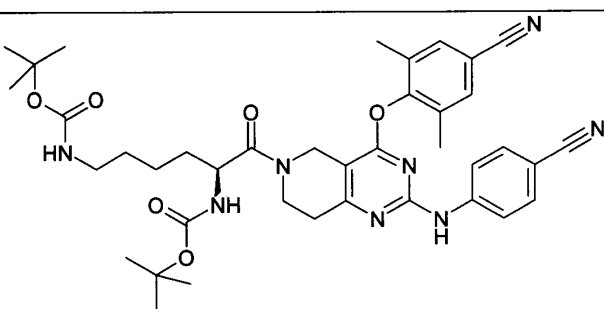
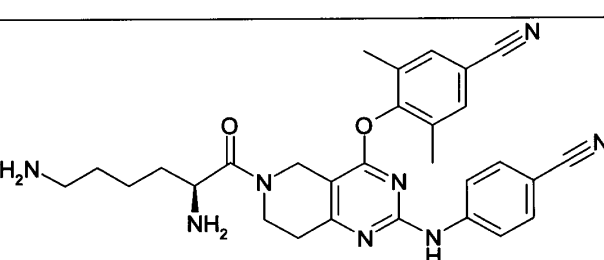
0274100		4-((2-((4-Cyanophenyl)amino)-6-(pyrazine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274101		(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxopropane-2-yl)carbamate

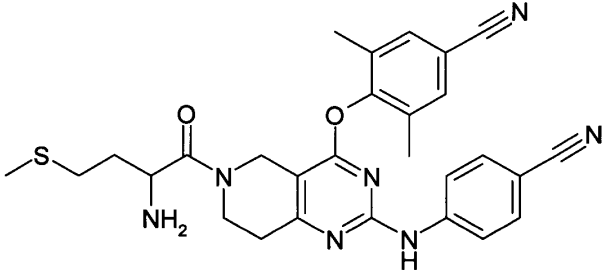
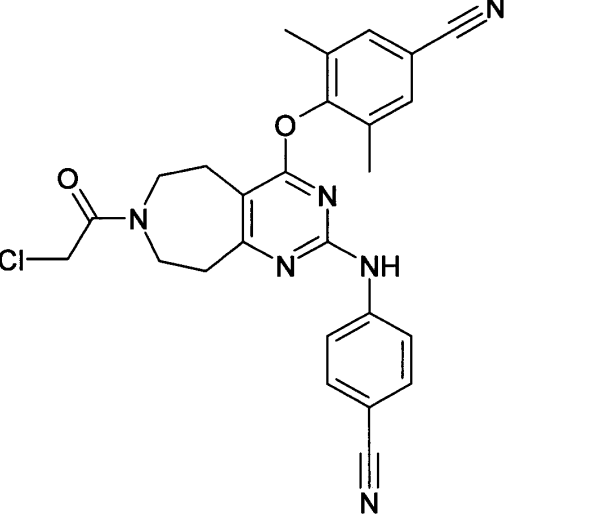
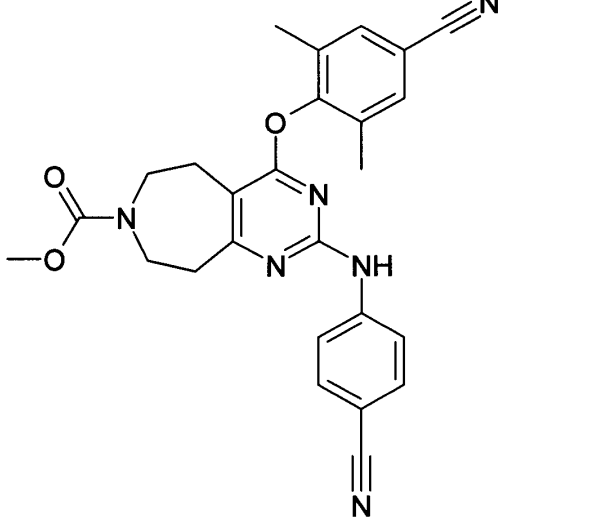
0274102		(S)-4-((6-(2-Aminopropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274103		(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxo-3-phenylpropane-2-yl)carbamate
0274111		(S)-4-((6-(2-Amino-3-phenylpropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

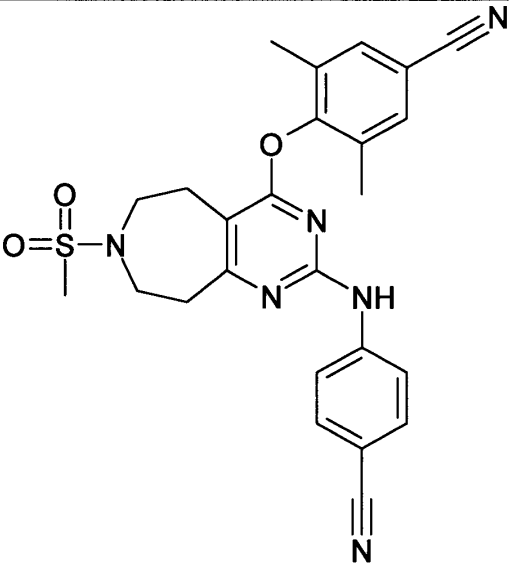
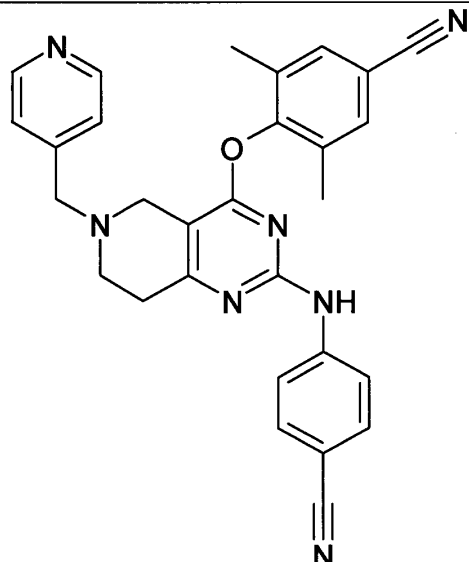
0274118		4-((2-((4-Cyanophenyl)amino)-7-(2-morpholineethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274119		(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-hydroxy-1-oxopropane-2-yl)carbamate
0274120		Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-(methylthio)-1-oxobutane-2-yl)carbamate

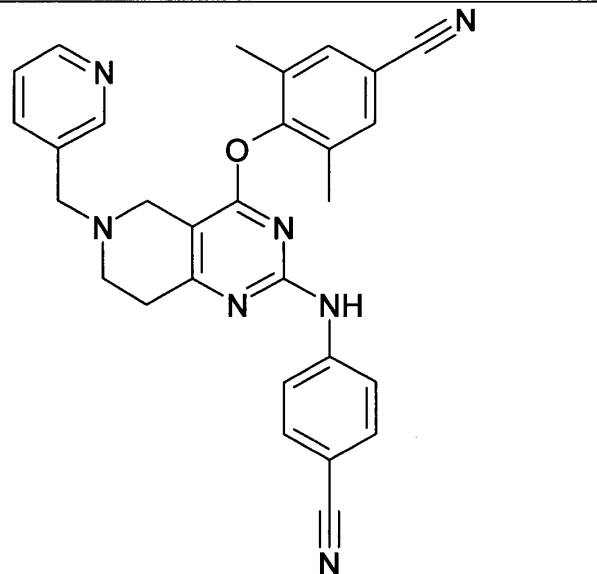
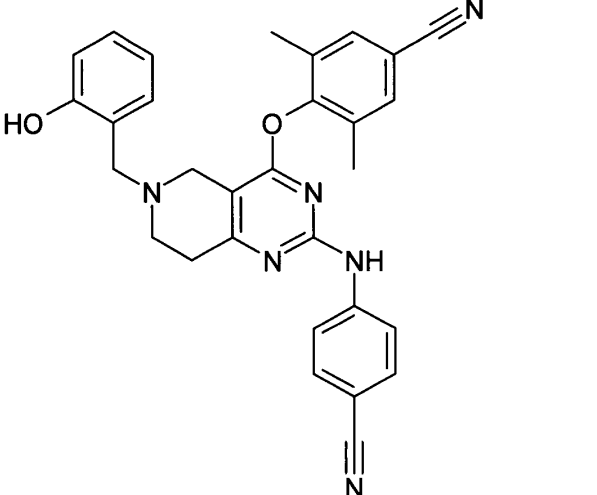
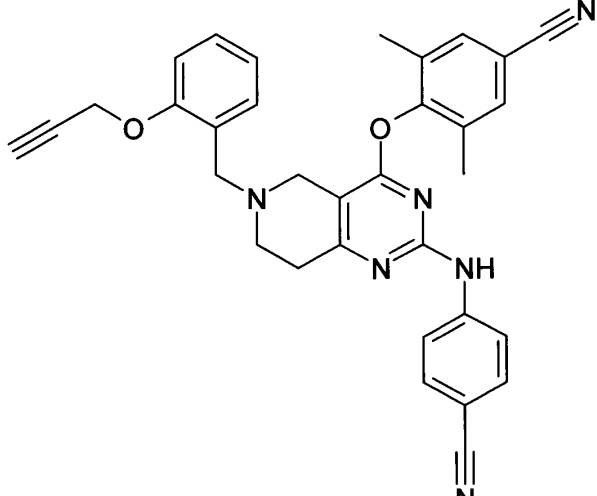
0275622		4-((6-[2-Amino-3-(1H-imidazole-5-yl)propanoyl]-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274121		4-((6-(2-Amino-3-(1H-pyrazole-4-yl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274122		Tert-butyl 4-(2-((tert-butoxycarbonyl)amino)-3-(4-(4-cyano-2,6-dimethylphenoxy))-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-oxopropyl)-1H-pyrazole-1-carboxylate

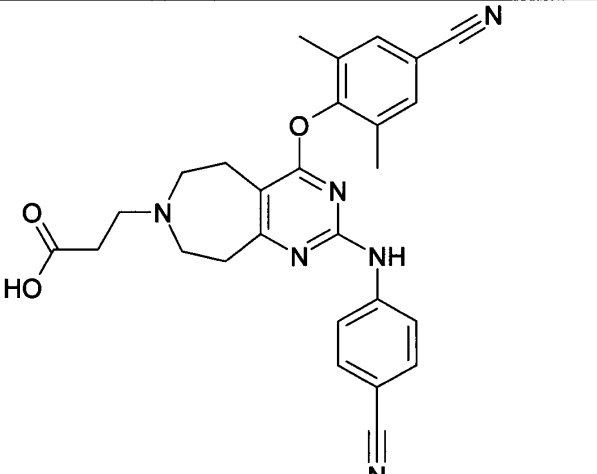
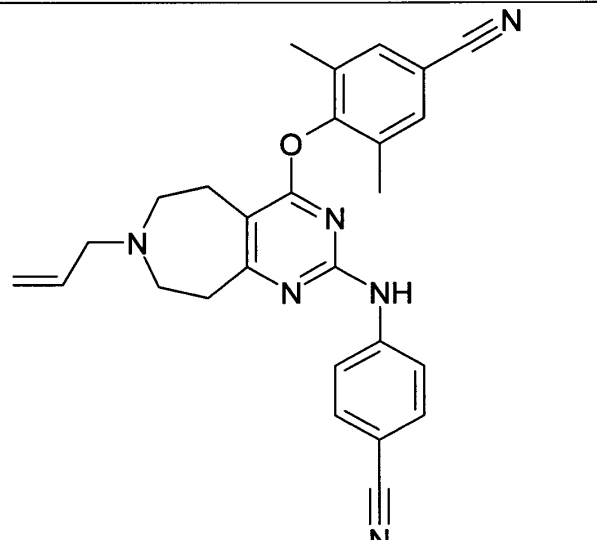
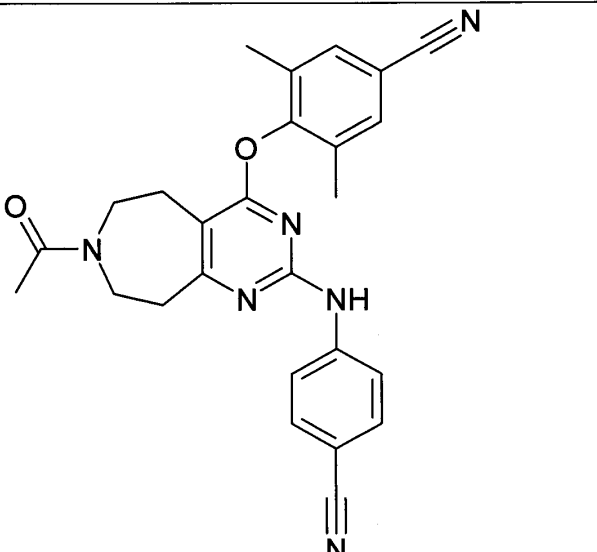
0274123		(R)-4-((6-(2-Amino-3-hydroxypropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274124		(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-(4-hydroxyphenyl)-1-oxopropane-2-yl)carbamate
0274125		(S)-4-((6-(2-Amino-3-(4-hydroxyphenyl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274126		(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-methyl-1-oxobutane-2-yl)carbamate

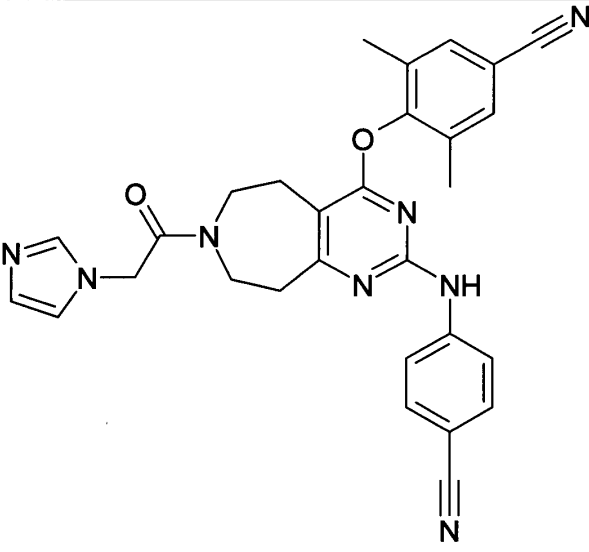
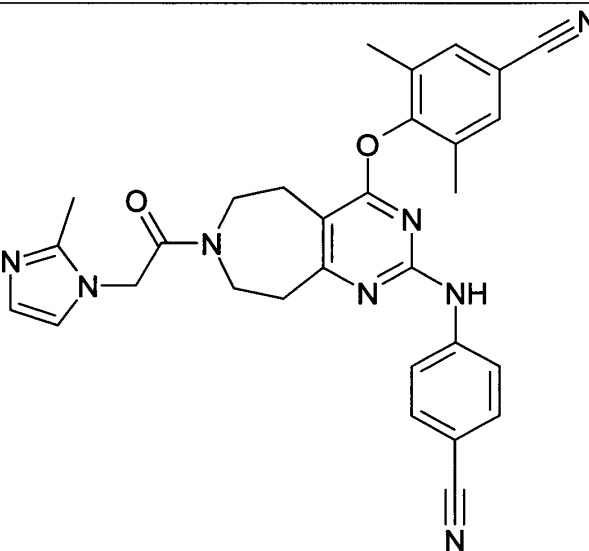
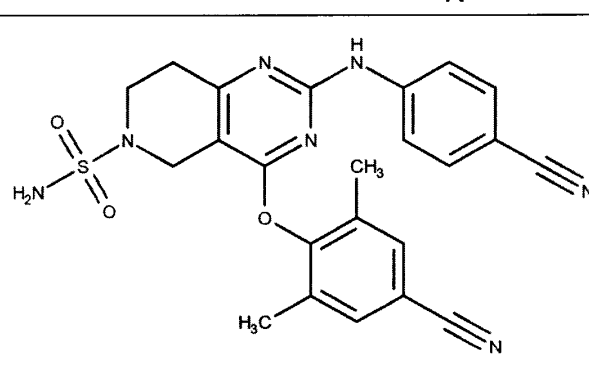
0274127		(R)-4-((6-(2-Amino-3-methylbutanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274128		(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-methyl-1-oxopentane-2-yl)carbamate
0274129		(S)-4-((6-(2-Amino-4-methylpentanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274130		(S)-Di-tert-butyl (6-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-6-oxohexane-1,5-diyl)dicarbamate
0274131		(S)-4-((2-((4-Cyanophenyl)amino)-6-(2,6-diaminohexanoyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

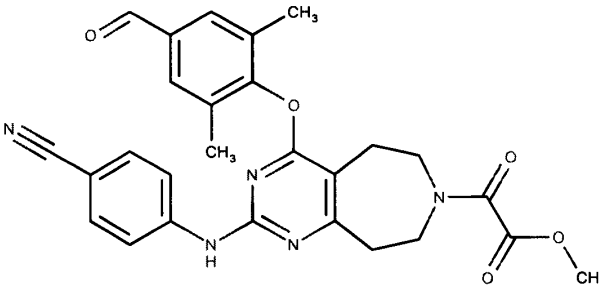
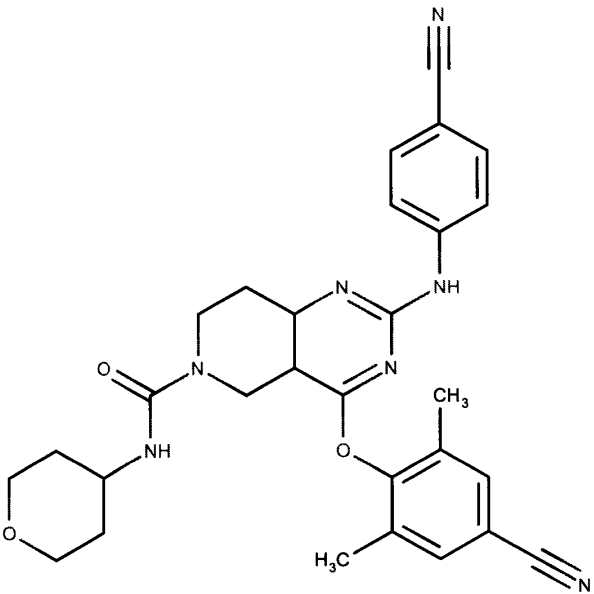
		dimethylbenzonitrile
0274132		4-((2-((4-cyanophenyl)amino)-6-methionyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile
0274133		4-((7-(2-chloroacetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274134		Methyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

0274135		4-((2-((4-Cyanophenyl)amino)-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274137		4-((2-((4-Cyanophenyl)amino)-6-(pyridine-4-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

0274138		4-((2-((4-Cyanophenyl)amino)-6-(pyridine-3-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274140		4-((2-((4-Cyanophenyl)amino)-6-(2-hydroxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274141		4-((2-((4-Cyanophenyl)amino)-6-(2-(prop-2-yn-1-yloxy)benzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

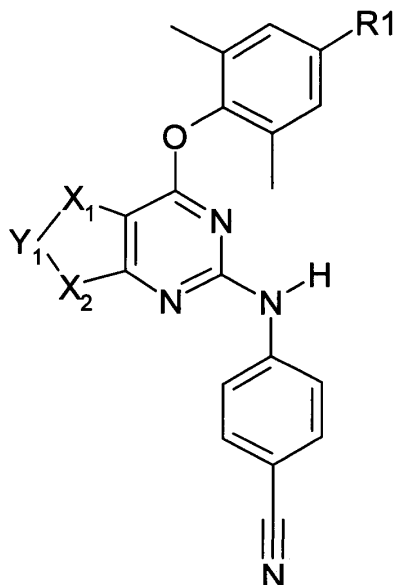
0274143		3-(4-(4-Cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)propanoic acid
0274144		4-((7-Allyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274145		4-((7-Acetyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

0274227		4-((7-(2-(1H-Imidazole-1-yl)acetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274236		4-((2-((4-Cyanophenyl)amino)-7-(2-(methyl-1H-imidazole-1-yl)acetyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
0274239		4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-6-sulfonamide

0274312		Methyl 2-{2-[(4-cyanophenyl)amino]-4-(4-formyl-2,6-dimethylphenoxy)-5H,6H,7H,8H,9H-pyrimido [4,5-d]azepine-7-yl}-2-oxoacetate
0274337		4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-N-(oxan-4-yl)-4aH,5H,6H,7H,8H,8aH-pyrido [4,3-d]pyrimidine-6-carboxamide

Detailed description of the Invention

In one embodiment, the present invention relates to a compound of formula I

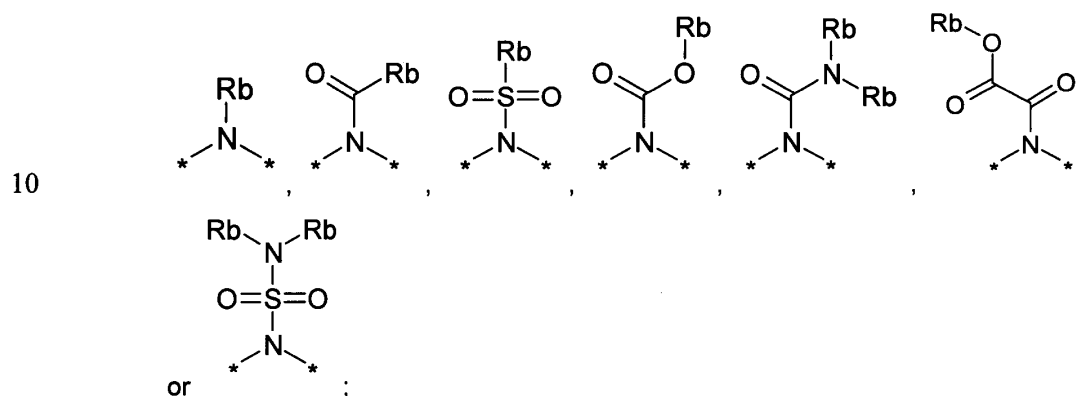


(I)

5 , where R¹ is independently selected and represents H-, -CN, CN-CH=CH-;

X¹, X² are substituents of (CH₂)_n type, wherein n is independently selected for X₁, X₂ and may have values from 1 to 3;

Y¹ is independently selected and represents -O-, -S-, -S(=O)-, -S(=O)₂-, or substituents of the following type:

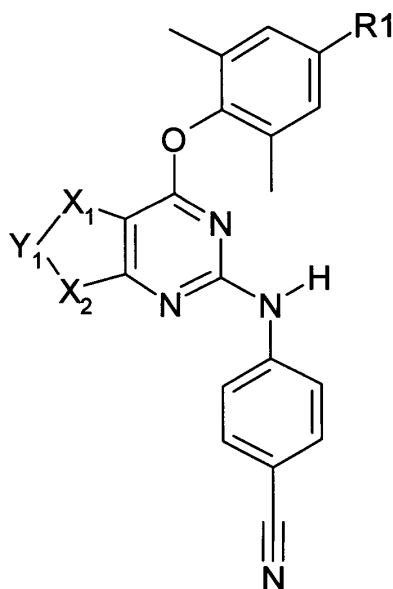


15 R^b is independently selected and represents -H, substituted or unsubstituted -C₁-C₆-alkyl, substituted or unsubstituted -C₁-C₆-alkenyl, substituted or unsubstituted -C₆-aryl, substituted or unsubstituted -5-6-membered-heteroaryl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O, substituted or unsubstituted -C₃-C₉-cycloalkyl, or substituted or unsubstituted 4-9-membered heterocyclyl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O; or pharmaceutically

acceptable salts thereof,

Wherein R^b may be attached to the remaining part of the molecule through a linker of $(CH_2)_n$ type, n is selected from 1 to 3.

In another embodiment, the invention relates to a compound of formula I

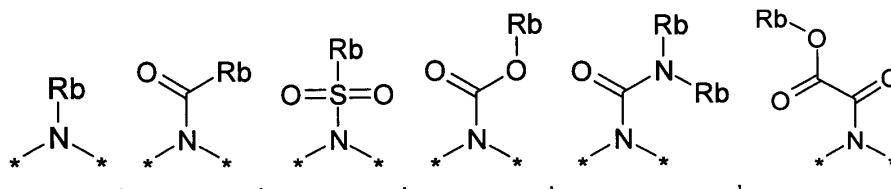


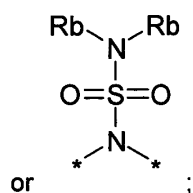
(1),

wherein R^1 is independently selected and represents H, CN, $CN-CH=CH$, $C=O$, $CH=CH-COOH$, substituted or unsubstituted 4-6-membered heterocyclyl, containing 1-2 heteroatom O; aminocarbonyl; NH_2 ; substituted or unsubstituted C_{1-6} alkyl; halogen; substituted or unsubstituted C_{1-6} alkyloxy; NHR^9 ; NR^9R^{10} ; $-C(=O)-NHR^9$; $-C(=O)-NR^9R^{10}$; $-C(=O)-R^9$; $-CH=N-NH-C(=O)-R^9$; substituted or unsubstituted C_{1-6} alkyloxy C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted C_{2-6} alkynyl; $-C(=N-O-R^8)-C_{1-4}$ alkyl; R^7 and $-R^b-R^7$;

X^1 , X^2 are substituent of $(CH_2)_n$ type, wherein n is independently selected for X_1 , X_2 ;

Y^1 is independently selected and represents $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, or substituents of the following type:





R^b is selected independently and represents -H, cyano, aminocarbonyl, substituted or unsubstituted -C₁-C₆-alkyl, substituted or unsubstituted -C₂-C₆-alkenyl, substituted or unsubstituted -C₂-C₆-alkynyl, substituted or unsubstituted -C₃-C₆-aryl, substituted or unsubstituted 4-6-membered-heteroaryl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O, substituted or unsubstituted -C₃-C₉-cycloalkyl, substituted or unsubstituted 4-9-membered heterocyclyl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O, R^7 or R^9 ,

wherein R^b may be attached to the remaining part of the molecule through a linker of $(\text{CH}_2)_n$ type

R^7 - is a monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic carbocycle or monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic 4-6 membered heterocycle, containing from 1 to 4 heteroatoms, independently selected from S, N and O, wherein each of said carbocycle or heterocycle may be optionally substituted by one, two, three, four or five substituents, each of which is independently selected from halogen, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- and di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl, -C(=N-O-R⁸), R^{7a} , -R^b- R^{7a} , and R^{7a} -C₁₋₄alkyl;

R^{7a} is a monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic carbocycle or monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic 4-6 membered heterocycle, containing from 1 to 4 heteroatoms, independently selected from S, N and O, wherein each of said carbocycle or heterocycle may be optionally substituted by one, two, three, four or five substituents, each of which is independently selected from halogen, hydroxy, mercapto, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, formyl, C₁₋₆alkylcarbonyl, C₃₋₇cycloalkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylthio, cyano, nitro, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, aminocarbonyl and -CH(=N-O-R⁸);

R^8 is hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl.

Each of R^9 and R^{10} is independently hydrogen; cyano, aminocarbonyl, hydroxy

group; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; -CH(=NR¹¹) or R⁷, wherein each of said C₁₋₆alkyl may be optionally, independently, substituted by one or two substituents, each of which is independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, aminocarbonyl, imino, mono- and di(C₁₋₆alkyl)amino, polyhalomethyl, polyhalomethyloxy; polyhalomethylthio, -S(=O)_pR⁸, -NH-S(=O)_pR⁸, -C(=O)R⁸, -NHC(=O)H, -C(=O)NHNH₂, NHC(=O)R⁸, C(=NH)R⁸, R⁷

wherein substituents of R¹, R^b each independently is selected from the group, comprising: COO-isobutyl, OH, CN, NH₂, C1-4-alkoxy, C1-4alkyl, 4-6-membered heteroaryl, containing from 1 to 4 heteroatoms, independently selected from S, N and O, wherein said heteroaryl is unsubstituted or substituted by CN, NH₂, OH, C1-6-alkyl, O or R^c; BOC, COOH, R^c, C3-6-aryl optionally substituted by CN, NH₂, OH, O or OCH₂C≡CH, 4-6-membered heterocyclyl containing 1-3 heteroatom selected from N, S and O, O, N, S-C1-6-alkyl, halogen, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl.

R^c represents NHCOO-C1-6-alkyl,
n may have values from 1 to 3.

In further embodiment, the invention relates to a compound as defined above, wherein R¹ is independently selected and represents H, CN, CN-CH=CH, C=O, CH=CH-COOH, 4-6-membered heterocyclyl, containing 1-2 heteroatom O;

R^b is independently selected and represents:

-H,

substituted or unsubstituted -C₁-C₆-alkyl,

substituted or unsubstituted -C₁-C₆-alkenyl,

substituted or unsubstituted -C₃-C₆-aryl,

substituted or unsubstituted 5-6-membered-heteroaryl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O,

substituted or unsubstituted -C₃-C₉-cycloalkyl, or

substituted or unsubstituted 4-9-membered heterocyclyl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O,

wherein substituents R^b mentioned above each is independently selected from a group, comprising:

COO-isobutyl,

NH₂,

CN,

C1-4-alkoxy,

4-6-membered heteroaryl, containing from 1 to 4 heteroatoms, independently selected from S, N and O, wherein said heteroaryl is unsubstituted or substituted with OH, C1-6-alkyl, O or Rc;

BOC;

5 COOH;

R^c ;

C3-6-aryl, optionally substituted with OH, O or OCH₂C≡CH,

4-6-membered heterocyclyl, containing 1-2 heteroatom, selected from N and O,

10 O, N,

S-C1-6-alkyl,

halogen,

The remaining substituents are defined in the present invention.

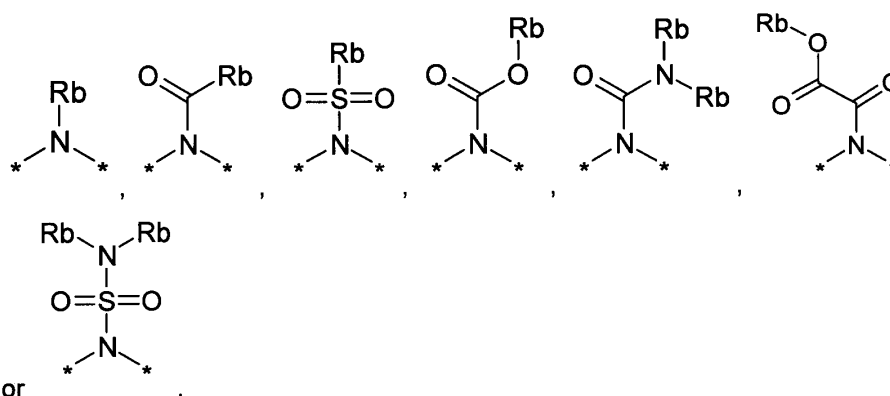
15 In another embodiment, the invention relates to a compound of the present invention, wherein R¹ is independently selected and represents H, -CN, -CH=CH-CN, -C=O or -CH=CH-COOH.

In another embodiment, the invention relates to a compound of the present invention, wherein R¹ is independently selected and represents 4-6-membered heterocyclyl, containing 1-2 heteroatoms O.

In another embodiment, the invention relates to the compound of the present invention, wherein R¹ is oxetane, tetrahydrofuran or tetrahydropyran.

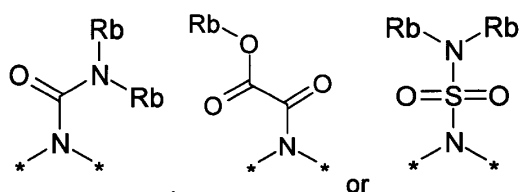
In another embodiment, the invention relates to a compound of the present invention, wherein Y¹ is -O-, -S-, -S(=O)- or -S(=O)₂-.

25 In another embodiment, the invention relates to a compound of the present invention, wherein Y¹ is substituents of the following type:



In another embodiment, the invention relates to a compound of the present

invention, wherein Y¹ is substituents of the following type:



In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted methyl, ethyl, propyl, n-propyl, isopropyl, butyl, n-butyl, sec-butyl, tert-butyl or pentyl, wherein substituents are defined in the present invention.

In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, wherein substituents are defined in the present invention.

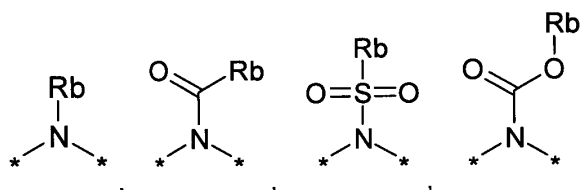
In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted phenyl, wherein substituents are defined in the present invention.

In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazolyl, benzo[b]thienyl, isobenzofuranyl, isoindolile, benzimidazolyl, wherein substituents are defined in the present invention.

In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.2]octanyl, spiro[5.5]undecanyl, wherein substituents are defined in the present invention.

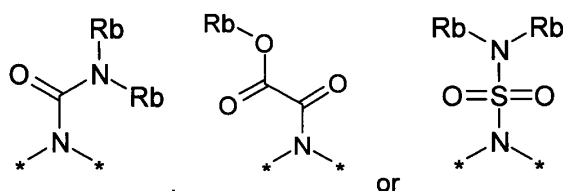
In another embodiment, the invention relates to a compound of the present invention, wherein Rb is substituted or unsubstituted pyrimidine, piperidine, azetidine, morpholine, piperazine, pyrrolidine, tetrahydropyran, furan, pyrrol, pyrazine, imidazole or pyrazole.

In another embodiment, the invention relates to a compound of the present invention, wherein Y¹ is substituents of the following type:



unsubstituted 5-6-membered-heteroaryl or heterocyclyl, containing from 1 to 4 heteroatoms, independently selected from N, S and/or O, wherein substituents are defined in the present invention.

In another embodiment, the invention relates to a compound of the present invention, wherein Y¹ is substituents of the following type:



, and Rb is substituted or unsubstituted -C₃-C₆-aryl or substituted or unsubstituted -C₃-C₉-cycloalkyl, wherein substituents are defined in the present invention.

In another embodiment, the invention relates to a compound selected from:

4-((4-(2,6-Dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-yl)amino)-benzonitrile

4-(2,6-Dimethylphenoxy)-N-(piperidine-4-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine

Ethyl ether 4-(((6-benzyl-4-(4-cyano-2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid

Ethyl ether 4-(((6-benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid

4-(((7-Benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)methyl)benzonitrile

N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydroquinazoline-2-amine

N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine

4-((2-((4-Cyanophenyl)amino)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine -4-yl)oxy)-3,5-dimethylbenzonitrile

4-((4-(4-Formyl-2,6-dimethylphenoxy)-7-methyl-5,6,7,8-tetrahydro[3,4-d]pyrimidine -2-yl)amino)benzonitrile

Tert-butyl 4-(4-(1,3-dioxolane-2-yl)-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-formyl-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-

dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

Ethyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

(E)-3-(4-((7-(Tert-butoxycarbonyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylphenyl)acrylic acid

Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-(2-cyanovinyl)-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-picolynoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-isonicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-nicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-2-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-3-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-4-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)piperidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)piperidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-yl)-6,7,8,9-tetrahydro-5H-

pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((6-(2-Aminoacetyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-6-(2-(3-hydroxyazetidine-1-yl)acetyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-6-[2-(morpholine-4-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-6-[2-(4,4-difluoropiperidine-1-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-7-(cyclopropanecarbonyl)-5,6,7,8-tetrahydro[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-6-(morpholine-4-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-6-(4-methylpiperazine-1-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile
Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate
(R)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate
(S)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate
4-((2-((4-Cyanophenyl)amino)-7-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-7-(5-methylfuran-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-7-(1-methyl-1H-pyrrol-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-7-(4-hydroxybenzyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
4-((2-((4-Cyanophenyl)amino)-7-(1-methoxypropane-2-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-6-carbonyl)pyrrolidine-1-carboxylate
4-((2-((4-Cyanophenyl)amino)-6-(pyrrolidine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((6-(Azetidine-3-carbonyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyrazine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxopropane-2-yl)carbamate

(S)-4-((6-(2-Aminopropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxo-3-phenylpropane-2-yl)carbamate

(S)-4-((6-(2-Amino-3-phenylpropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(2-morpholinoethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-hydroxy-1-oxopropane-2-yl)carbamate

Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-(methylthio)-1-oxobutane-2-yl)carbamate

4-((6-[2-Amino-3-(1H-imidazole-5-yl)propanoyl]-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((6-(2-Amino-3-(1H-pyrazole-4-yl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(2-((tert-butoxycarbonyl)amino)-3-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-oxopropyl)-1H-pyrazole-1-carboxylate

(R)-4-((6-(2-Amino-3-hydroxypropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-(4-hydroxyphenyl)-1-oxopropane-2-yl)carbamate

(S)-4-((6-(2-Amino-3-(4-hydroxyphenyl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-methyl-1-oxobutane-2-yl)carbamate

(R)-4-((6-(2-Amino-3-methylbutanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-methyl-1-oxopentane-2-yl)carbamate

(S)-4-((6-(2-Amino-4-methylpentanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Di-tert-butyl (6-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-6-oxohexane-1,5-diyl)dicarbamate

(S)-4-((2-((4-Cyanophenyl)amino)-6-(2,6-diaminohexanoyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-(2-Chloroacetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Methyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl) amino)-8,9-dihydro-5H- pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyridine-4-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyridine-3-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(2-hydroxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(2-(prop-2-in-1-yloxy)benzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

3-(4-(4-Cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H- pyrimido[4,5-d]azepine-7(6H)-yl)propanoic acid

4-((7-Allyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H- pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-Acetyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-(2-(1H-Imidazole-1-yl)acetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-

tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
 4-((2-((4-Cyanophenyl)amino)-7-(2-(methyl-1H-imidazole-1-yl)acetyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile
 4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-6-sulfonamide
 Methyl 2-{2-[(4-cyanophenyl)amino]-4-(4-formyl-2,6-dimethylphenoxy)-5H,6H,7H,8H,9H-pyrimido [4,5-d]azepine-7-yl}-2-oxoacetate
 4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-N-(oxane-4-yl)-4aH,5H,6H,7H,8H,8aH-pyrido [4,3-d]pyrimidine-6-carboxamide

In another embodiment, the invention relates to a compound of the present invention, which comprises at least one isotope.

In another embodiment, the invention relates to a compound of the present invention in the form of:

a free base,

or a pharmaceutically acceptable salt selected from a group, comprising salts of amino groups formed by inorganic acids, such as hydrochloric, hydrobromic, phosphoric, sulfuric and chloric acids, or formed by organic acids, such as acetic, oxalic, maleic, tartaric, succinic or malonic acids,

or pharmaceutically acceptable salts: adipate, alginate, ascorbate, aspartate, benzene sulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphor sulfonate, citrate, cyclopentanepropionate, digluconate, dodecyl sulfate, ethane sulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethane sulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalene sulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate,

or a pharmaceutically acceptable salt, containing alkaline and/or alkaline-earth metals, or nontoxic cations of ammonium, quaternary ammonium and amine,

or a pharmaceutically acceptable salt obtained using counterions, such as halogenides, hydroxides, carboxylates, sulfates, phosphates, nitrates, lower alkyl sulfates and aryl sulfonates.

In another embodiment, the invention relates to a compound of the present invention for use as reverse transcriptase inhibitor.

In another embodiment, the invention relates to a compound of the present

invention for use as a pharmaceutical preparation, having anti-HIV antiviral activity.

In another embodiment, the invention relates to a compound of the present invention for obtaining a pharmaceutical preparation, having anti-HIV antiviral activity.

In another embodiment, the invention relates to a pharmaceutical composition,
5 modulating the reverse transcriptase activity, comprising the compound of the present invention in a therapeutically effective amount and at least one carrier, excipient or diluent.

In another embodiment, the invention relates to a pharmaceutical composition for the treatment or prevention of HIV, comprising at least one compound of the present
10 invention in a therapeutically effective amount and at least one carrier, excipient or diluent.

In another embodiment, the invention relates to a pharmaceutical composition, modulating the HIV reverse transcriptase activity, comprising the compound of the present invention in a therapeutically effective amount, and at least one compound,
15 selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors.

In another embodiment, the invention relates to a pharmaceutical composition, modulating the HIV reverse transcriptase activity, wherein HIV reverse transcriptase has
20 at least one mutation compared to Wild type HIV, comprising the compound of the present invention in a therapeutically effective amount.

In another embodiment, the invention relates to a pharmaceutical composition, modulating the HIV reverse transcriptase activity, wherein HIV reverse transcriptase has reduced sensitivity to the following drugs: Efavirenz, Nevirapine, Doravirine or
25 Delavirdine, comprising the compound of the present invention in a therapeutically effective amount.

In another embodiment, the invention relates to a pharmaceutical composition for obtaining an agent for the treatment or prevention HIV, comprising at least one compound of the present invention in a therapeutically effective amount, and a pharmaceutically
30 acceptable carrier.

In another embodiment, the invention relates to the use of compounds of the present invention for obtaining an agent for the treatment or prevention of HIV.

In another embodiment, the invention relates to the use of the composition of the present invention for obtaining an agent for the treatment or prevention of HIV.

35 In another embodiment, the invention relates to a method for the treatment or prevention of HIV, comprising the use of at least one compound of the present invention.

In another embodiment, the invention relates to a method for the treatment or prevention of HIV, comprising the use of the composition of the present invention.

In another embodiment, the invention relates to a method for the treatment or prevention of HIV infection, wherein a therapeutically effective amount of at least one
5 compound of the present invention is administered to the subject as needed for such treatment.

In another embodiment, the invention relates to the abovementioned method for the treatment or prevention, wherein said therapeutically effective amount of compounds means a daily dose, which is approximately 0.1 to approximately 500 mg/kg body weight
10 in parenteral infusion.

In another embodiment, the invention relates to the abovementioned method for the treatment or prevention, wherein daily dose may be administered as a single dose or 1-5 separate doses.

In another embodiment, the invention relates to a combination for the treatment or prevention of HIV-mediated diseases, comprising therapeutically effective amount of
15 compounds of the present invention and at least one compound, selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors.

In another embodiment, the invention relates to a method for the treatment or prevention of HIV-mediated diseases, wherein a therapeutically effective amount of compounds of the present invention and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists, and viral cell entry
20 inhibitors is administered to a subject in need of such treatment.

In another embodiment, the invention relates to a reverse transcriptase inhibition method in a body of an HIV infected subject, wherein a therapeutically effective amount of at least one compound of the present invention is administered to the subject as needed for such treatment.

In another embodiment, the invention relates to a method of obtaining a pharmaceutical composition of the present invention, comprising mixing of compounds of the present invention with pharmaceutically acceptable carriers.
30

The term "As mentioned above" means the widest definition of each group specified in section *Summary of Invention* or in the widest claim of the claims of invention
35 or in the present specification. In other embodiments provided below, substituents are present in each variant, which optionally maintain the most general volume specified in

section *Summary of Invention* or in the present specification.

Unless otherwise stated, technical and scientific terms used in the description of the present invention have meanings known to a specialist in the prior art, to which the invention refers. The description comprises references to different procedures and materials known to a skilled in the art. Standard document, wherein pharmacology common factors are considered, is monograph: Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, 13 ed., McGraw Hill Companies Inc., New York (2017). In the context of this invention, any suitable materials and/or methods may be used known to a skilled in the art. However, the specification of the present invention contains description of preferable materials and methods. Materials, reagents, etc. mentioned in the specification and in examples, are commercial products, unless otherwise stated.

The term "Compound of the present invention" or "compound according to the invention" mentioned herein refers to at least one compound mentioned in the present invention, as well as to any combination of them, including double combination, triple combination, etc.

In the specification of the invention, for example, in any section of the application or in the invention claims, the terms "includes (include)" and "including" have conventional meaning. I.e. the terms approximately correspond to "containing at least" or "including at least" provisions. As for the method, the term "including" means that the method includes at least the mentioned stages. As for compounds or compositions, the term "including" means that a compound or composition includes at least the abovementioned features or components; however, it may also include additional features or components.

The term "approximately" used in the specification means approximately, about, around or roughly. The term "approximately" used in relation to number interval means that maximal and minimal values of the interval have the abovementioned values. In general, the term "approximately" is used to specify acceptable changes of the numerical value 20% higher and lower than the value specified.

It is entailed that numerical value interval used in the description specification means that the invention may be used at any value within the specified interval. Thus, a variable, which is discrete by nature, may have any integral value within the mentioned interval, including final values of the interval. Likewise, a variable, which is continuous by nature, may have any actual value within the interval specified, including final values of the interval. For example, a variable, which according to the specification have values between 0 and 2, may mean 0, 1 or 2, if this is a discrete value, and may have values of 0.0, 0.1, 0.01, 0.001, or any actual value, if this is a continuous variable.

If any group (for example, R¹) is contained in a fragment content or in any formula mentioned or in any compound described more than two times, and described compounds are used or claimed in this invention, then its value in each case is independent. Moreover, combinations of substituents and/or variables are allowed in
5 such a case only if obtained compounds are stable compounds.

In one embodiment of the present invention, a compound of formula I is proposed, wherein R¹, X¹, X², Y¹ have the abovementioned values. The terms "abovementioned", "as mentioned above" and "said" mean variables included in the form of a reference in the widest definition of variables mentioned in section *Summary of invention* or in the
10 widest claim of the invention specification.

In one more embodiment of the present invention, a compound is proposed, which represents free base or pharmaceutically acceptable salt compounds according to the present invention.

In another embodiment of the present invention, a method for the treatment of HIV
15 infection or prevention of HIV infection is proposed, which consists of a subject in need for treatment being administered with a therapeutically effective amount of compounds of formula I, wherein R¹, X¹, X², Y¹ have the abovementioned values.

In one more embodiment of the present invention, a method for the treatment or prevention of HIV-mediated diseases is proposed, which consists of a subject in need for
20 treatment being administered with a therapeutically effective amount of compounds of formula I, wherein R¹, X¹, X², Y¹ have the abovementioned values, and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors.

25 In another embodiment of the present invention, a method of inhibition of HIV reverse transcriptase in the body of a HIV infected subject is proposed, which consists in a subject in need for treatment being administered with a therapeutically effective amount of compounds of formula I, wherein R¹, X¹, X², Y¹ have the abovementioned values.

In another embodiment of the present invention, a method of inhibition of HIV
30 reverse transcriptase in the body of a HIV infected subject is proposed, wherein HIV reverse transcriptase contains at least one mutation compared to Wild type HIV, which consists of a subject in need for treatment being administered with a therapeutically effective amount of compounds of formula I, wherein R¹, X¹, X², Y¹ have the abovementioned values.

35 In another embodiment of the present invention, a method of inhibition of HIV reverse transcriptase in the body of a HIV infected subject is proposed, wherein HIV

reverse transcriptase has reduced sensitivity to Efavirenz, Nevirapine or Delavirdine products, which consists of a subject in need for treatment being administered with a therapeutically effective amount of compounds of formula I, wherein R^1 , X^1 , X^2 , Y^1 have the abovementioned values.

- 5 In one embodiment of the present invention, a pharmaceutical composition is proposed, comprising the compound of formula I, wherein R^1 , X^1 , X^2 , Y^1 have the abovementioned values, and at least one carrier, excipient or diluent.

 The following definitions are used in this document, if not otherwise clearly stated. Moreover, unless otherwise stated, all inclusions of functional groups are selected
10 independently, two inclusions may be both the same, and different.

The term «alkyl» on its own or as a part of another substituent refers to saturated hydrocarbon groups with linear or branched chain, including hydrocarbon groups, having the stated number of carbon atoms (i.e., C_{1-6} -alkyl assumes between one and six carbon atoms). Examples of alkyls include methyl, Ethyl, n-propyl, iso-propyl.

- 15 **The term «alkynyl»** on its own or as a part of another substituent refers to hydrocarbon groups, wherein at least one carbon-carbon bond is a triple bond, while the rest of bonds may be single, double or additional triple bonds, including hydrocarbon groups, between 2 and 6 carbon atoms. Examples of alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, etc.

- 20 The term **«alkenyl»** on its own or as a part of another substituent refers to hydrocarbon groups, wherein at least one carbon-carbon bond is a double bond, while the rest of bonds may be either single bonds, or additional double bonds, including hydrocarbon groups, containing between 2 and 6 carbon atoms. Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-
25 1-propenyl, 2-methyl-2-propenyl, etc.

 The term **«halogen»** on its own or as a part of another term refers to atoms of fluorine, chlorine, bromine, or iodine.

 The terms «carboxyl», «carboxy» or «hydroxycarbonyl» refer to -COOH group.

- The terms «alkoxy» and «alkyloxy» on their own or in word combinations refer (if
30 not otherwise stated) to aliphatic radicals of alkyl-O- type, wherein alkyl is determined above. Illustrative examples of alkoxy-groups include (but not limited to those listed) methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, tert-butoxy-, pentoxy-, isopentoxy-, neopentoxy-, tert-pentoxy-, hexoxy-, isohexoxy-, heptoxy-, octoxy-group, etc. Preferable alkoxy-groups are methoxy- and ethoxy-group.

- 35 Monocyclic, bicyclic or tricyclic saturated carbocycle represents a cyclic system, consisting of 1, 2 or 3 cycles; wherein, the specified cyclic system consists of carbon

atoms only, and the specified cyclic system contains single bonds only; monocyclic, bicyclic, or tricyclic partially saturated carbocycle represents cyclic system, consisting of 1, 2 or 3 cycles; wherein, the specified cyclic system consists of carbon atoms only and includes at least double bond, given that cyclic system is not an aromatic cyclic system;

5 monocyclic, bicyclic, or tricyclic aromatic carbocycle represents aromatic cyclic system, consisting of 1, 2 or 3 cycles; wherein, the specified cyclic system consists of carbon atoms only; the term "aromatic" is well known to specialists in the prior art, and it means cyclic conjugated system, including $4n+2$ electrons, i.e. 6, 10, 14 etc. π -electrons (Huckel's rule); monocyclic, bicyclic or tricyclic saturated heterocycle represents cyclic

10 system, consisting of 1, 2 or 3 cycles and including at least one heteroatom selected from O, N or S; wherein, the specified cyclic system contains single bonds only; monocyclic, bicyclic, or tricyclic partially saturated heterocycle represents cyclic system, consisting of 1, 2 or 3 cycles and including at least one heteroatom selected from O, N or S, and at least one double bond, given that cyclic system is not an aromatic cyclic system;

15 monocyclic, bicyclic, or tricyclic aromatic heterocycle represents aromatic cyclic system, consisting of 1, 2 or 3 cycles and including at least one heteroatom selected from O, N or S.

Specific examples of monocyclic, bicyclic or tricyclic saturated carbocycles are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4,2,0]-

20 octanyl, cyclononanyl, cyclodecanyl, decahydronaphthalenyl, tetradecahydroanthracenyl, etc. Preferable are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, more preferable are cyclopentyl, cyclohexyl, cycloheptyl.

Specific examples of monocyclic, bicyclic or tricyclic partially saturated carbocycles are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[4,2,0]octenyl, cyclononenyl, cyclodecenyl, octahydronaphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2,3,4,4a,9,9a,10-

25 octahydroanthracenyl, etc.

Specific examples of monocyclic, bicyclic or tricyclic aromatic carbocycles are phenyl, naphthalenyl, anthracenyl. Phenyl is preferable.

30 Specific examples of monocyclic, bicyclic or tricyclic saturated heterocycles are tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl, tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl, triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyrazinyl, dioxanyl, morpholinyl, dithianyl, thiophorpholinyl, piperazinyl, trithianyl,

35 decahydroquinolinyl, octahydroindolyl, etc. Preferable are tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, thiazolidinyl, dihydrooxazolyl, triazolidinyl, piperidinyl, dioxanyl,

morpholinyl, thiomorpholinyl, piperazinyl. The most preferable are tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, piperidinyl, dioxanyl, morpholinyl, thiomorpholinyl, piperazinyl.

Specific examples of monocyclic, bicyclic and tricyclic partially saturated heterocycles are pyrrolinyl, imidazolinyl, pyrazolinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxynyl, indolinyl, etc. Preferable are the following: pyrrolinyl, imidazolinyl, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl, indolinyl.

Specific examples of monocyclic, bicyclic or tricyclic aromatic heterocycles are asetyl, oxetilidenyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolysinyl, indolyl, isoindolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, quinolinyl, isoquinolinyl, cinnolynyl, quinoliziny, phthalazinyl, quinoxaliny, quinazoliny, naphthyridiny, pteridiny, benzopyrany, pyrrolopyridyl, thienopyridyl, furopyridyl, isothiazolepyridyl, thiazolopyridyl, isoxazolopyridyl, oxazolopyridyl, pyrazolopyridyl, imidazopyridyl, pyrrolopyrazinyl, thienopyrazinyl, furopyrazinyl, isothiazole pyrazinyl, thiazole pyrazinyl, isoxazole pyrazinyl, oxazole pyrazinyl, pyrazole pyrazinyl, imidazopyrazinyl, pyrrolo-pyrimidinyl, thieno-pyrimidinyl, furopyrimidinyl, isothiazole pyrimidinyl, thiazole pyrimidinyl, isoxazole pyrimidinyl, oxazole pyrimidinyl, pyrazole pyrimidinyl, imidazopyrimidinyl, pyrrole pyridazinyl, thienopyridazinyl, furopyridazinyl, isothiazole pyridazinyl, thiazole pyridazinyl, isoxazole pyridazinyl, oxazole pyridazinyl, pyrazole pyridazinyl, imidazopyridazinyl, oxadiazole opyridyl, thiadiazole pyridyl, triazole pyridyl, oxadiazole pyrazinyl, thiadiazole pyrazinyl, triazole pyrazinyl, oxadiazole pyrimidinyl, thiadiazole pyrimidinyl, triazole pyrimidinyl, oxadiazole pyridazinyl, thiadiazole pyridazinyl, triazole pyridazinyl, imidazooxazolyl, imidazothiazolyl, imidazoimidazolyl, isoxazole triazinyl, isothiazole triazinyl, pyrazole triazinyl, oxazole triazinyl, thiazole triazinyl, imidazotriazinyl, oxadiazole triazinyl, thiadiazole triazinyl, triazole triazinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyle, phenoxazinyl, etc.

Preferable aromatic heterocycles are monocyclic or bicyclic aromatic heterocycles. Monocyclic, bicyclic, or tricyclic aromatic heterocycles of interest are pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, pyranyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzoxazolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benzopyrazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, xinolynyl,

isoxinolynyl, phthalazinyl, quinoxalynyl, quinazolinyl, benzopyranyl, pyrrole pyridyl, thienopyridyl, furopyridyl, isothiazole pyridyl, thiazole pyridyl, isoxazole pyridyl, oxazole pyridyl, pyrazole pyridyl, imidazopyridyl, pyrrolopyrazinyl, thienopyrazinyl, furopyrazinyl, isothiazole pyrazinyl, thiazole pyrazinyl, isoxazole pyrazinyl, oxazole pyrazinyl, pyrazole pyrazinyl, imidazopyrazinyl, pyrrolopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, isothiazole pyrimidinyl, thiazole pyrimidinyl, isoxazole pyrimidinyl, oxazole pyrimidinyl, pyrazole pyrimidinyl, imidazopyrimidinyl, oxadiazole pyridyl, thiadiazole pyridyl, triazole pyridyl, oxadiazole pyrazinyl, thiadiazole pyrazinyl, triazole pyrazinyl, oxadiazole pyrimidinyl, thiadiazole pyrimidinyl, triazole pyrimidinyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, etc.

The term «**cycloalkyl**» in this document refers to groups, having between 3 and 12 carbon atoms in mono- or polycyclic structure, including spirocycles. For purposes of illustration, cycloalkyls include, but are not limited to, the following radicals: cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.2]octanyl, spiro[5.5]undecanyl, which, as in case with other aliphatic or heteroaliphatic or heterocyclic substituents, may be substituted.

“**Heterocycle**”, “**heterocyclyl**” or «**heterocyclic**» mean in this document non-aromatic mono- or polycyclic systems (saturated or partially non-saturated), having between three and twelve atoms, containing heteroatoms N, O or S. Heterocycle may be attached to the main moiety through nitrogen atom (N-heterocyclyl) or through carbon atom. Heterocycles may also be substituted. In particular, heterocycle may represent, but not limited to, azipidinyl, oxyranyl, azetidiny, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, 1,1-dioxo-thiomorpholine-4-yl, azepanyl, diazepanyl, homopiperazinyl, oxazepanyl, 8-azabicyclo[3.2.1]octyl, quinuclidinyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 9-azabicyclo[3.3.1]nonyl, 3-oxa-9-azabicyclo[3.3.1]nonyl, or 3-thia-9-azabicyclo[3.3.1]nonyl. Specific examples of heterocycles are also dihydrofuryl, imidazoliny, dihydro-oxazolyl, tetrahydro-pyridinyl, dihydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and 2-oxa-5-aza-bicyclo[2.2.1]heptyl. The term “**cycloalkenyl**” means in this document partially non-saturated cycloalkyl, containing between 5 and 12 carbon atoms, having between one and two double carbon-carbon bonds.

The term “**aryl**” in this document means groups, containing aromatic cycle, having between five and ten carbon atoms. An example of aryl cyclic groups is phenyl and naphthyl.

The term “**heteroaryl**”, “**heteroaryl cycle**”, as it is used herein, means a stable

heterocyclic and polyheterocyclic aromatic fragment, having 5-10 atoms in a cycle. Heteroaryl group may be substituted or not substituted and may consist of one or several rings. Possible substituents include, among others, any from the abovementioned substituents. Examples of typical heteroaryl cycles are five- and six-membered
5 monocyclic groups, such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazolyl, etc.; as well as polycyclic heterocyclic groups, such as benzo[b]thienyl, isobenzofuranyl, isoindolyl, benzimidazolyl, etc. The term “heteroaryl” may be used equivalently to “heteroaryl cycle” or “heteroaromatic”.

Aryl group or heteroaryl group (including heteroaryl part of heteroaralkyls or
10 heteroaralkoxy moieties, etc.) may contain one or several substituents. Examples of suitable substituent on unsaturated carbon atom of aryl or heteroaryl groups include, but are not limited to, halogen (F, Cl, Br or I), C₁₋₃-alkyl, -CN, -OH, -C₁₋₃-alkyl and others, as specified in this invention.

Carbocycles or heterocycles mentioned in the definition of R⁷ or R^{7a} may be
15 attached to the rest of molecule of formula (I) through any suitable cyclic carbon atom or heteroatom if not otherwise specified. Thus, for example, if heterocycle represents imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, etc., or, if carbocycle represents naphthalenyl, it may be 1-naphthalenyl, 2-naphthalenyl, etc.

If any of substituents (for example, R⁷) at the same time is met in the same
20 compound more than once, each from the definitions of such a substituent is independent.

The term “**substituted**” shall mean that one or more hydrogen atom at atom or group mentioned as “substituted” is substituted by any of the listed groups, provided that the atom mentioned has normal valency, or that valency of the group atom being
25 substituted is not excessive, and that substitution results in a stable compound. The term “substituted or unsubstituted” means that this compound or substructure is either unsubstituted, or substituted, as defined in the application, by one or more substituents, as mentioned or as defined below.

In this document, alkyl, alkenyl, alkynyl, alkylene, cycloalkyl, cycloalkenyl,
30 heterocyclyl, aryl and heteroaryl groups, as well as other substructures, containing at least one hydrogen atom in their composition, may be substituted by one or more substituents:

-F, -Cl, -Br, -CN, -OH, -NO₂, -NH₂, -CF₃, -CHF₂, -CH₂F, -C₁-C₄-alkyl, -C₂-C₄-alkenyl, -C₂-C₄-alkynyl, -C₃-C₉-cycloalkyl, -4-9-membered-heterocyclyl attached through
35 C- or N-atoms, -phenyl, -5-6-membered-heteroaryl attached through C- or N-atoms, -O-R^z, -N(R^z)₂, -NR^z-C(=O)-R^z, -NR^z-S(=O)₂-R^z, -S-R^z, -C(=O)-R^z, -C(=O)-OR^z, -C(=O)-

$N(R^z)_2$, $-O-C(=O)-R^z$, $-O-C(=O)-(NR^z)_2$, $-SO-N(R^z)_2$, $-SO_2-R^z$, wherein each R^z is independently selected and represents $-H$, $-C_1-C_6$ -alkyl, $-C_3-C_9$ -cycloalkyl, $-5-6$ -membered heteroaryl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O, or substituted or unsubstituted 4-9-membered heterocyclyl, containing 1 to 4 heteroatoms;

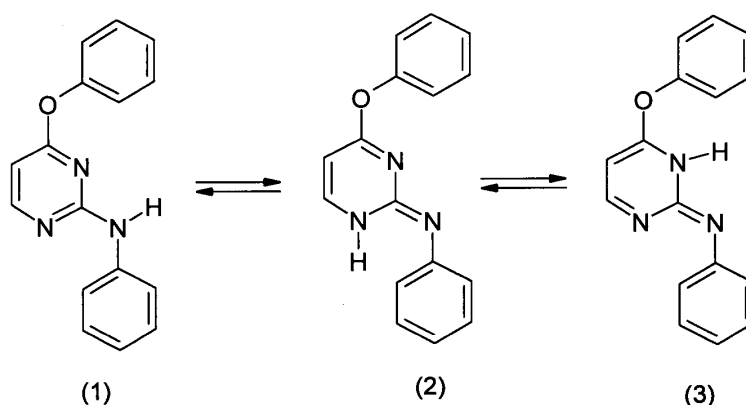
Another group, from which substituents may be selected, represents:

COO-isobutyl, NH_2 , CN, C_{1-4} -alkoxy, 4-6-membered heteroaryl, containing 1 to 4 heteroatoms, independently selected from a group S, N and O (17,18, 67,45, 60), in addition, the abovementioned heteroaryl is unsubstituted or substituted with $-OH$, C_{1-6} -alkyl, O, or R^c ; BOC, COOH, R^c , C_{3-6} -aryl, optionally substituted OH, O or $OCH_2C\equiv CH$, 4-6-membered heterocyclyl, containing 1-2 heteroatom selected from N and O, O, nitrogen atom, S- C_{1-6} -alkyl, halogen. This invention contains such only combinations of substituents and derivatives, which form stable or chemically possible compound. Stable or chemically possible compound is a compound, the stability of which is sufficient for its synthesis and analytical detection. Preferable compounds of the present invention are stable enough and do not degrade at the temperature up to 40 °C in the absence of chemically active conditions for at least one week.

Some compounds of the present invention may exist in tautomeric forms, and this invention includes such tautomeric forms of such compounds, unless otherwise stated.

For example, compounds of the present invention may exist in the form of tautomers 1-3, being in a state of dynamic balance. Under normal conditions, their separation is not possible, thus, pharmacological prosperities of compounds of the present invention represent a complex of effects of tautomers.

An example of tautomeric forms of compounds according to the invention represents:



If not otherwise stated, structures shown herein also assume all stereoisomers, i.e. R- and S-isomers for each asymmetric center. Moreover, some stereochemical

isomers, likewise enantiomers and diastereomeric mixtures of these compounds, are also a subject of the present invention. Thus, this invention covers each diastereomer or enantiomer, significantly free from other isomers (>90%, preferably >95% molar purity), as well as the mixture of such isomers.

5 A specific isomer may be obtained by the separation of racemic mixture according to the standard procedure, for example, by obtaining diastereomeric salts by exposing to optically active acid or base followed by the separation of the mixture of diastereomers by crystallization with further isolation of optically active bases from these salts. Examples of such acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluene tartaric and
10 camphorsulfonic acid. Another procedure of separation of optic isomers consists in the use of chiral chromatographic column. Moreover, another method of separation includes synthesis of covalent diastereomeric molecules by the reaction of invention compounds with optically pure acid in an activated form or by optically pure isocyanate. Obtained diastereomers may be separated using general methods, for example, chromatography,
15 distillation, crystallizations or sublimation, and then hydrolyzed to obtain enantiomerically pure compounds.

Optically active compounds of the present invention may be obtained using optically active initial materials. Such isomers may be in the form of free acid, free base, ester or salt.

20 This invention includes all pharmaceutically acceptable isotopically-labelled compounds according to this invention, wherein one or several atoms is substituted by atoms, having the same atomic number, but atomic weight or mass number different from those usually met in nature.

Examples of isotops suitable for the inclusion into compounds according to the
25 invention include isotops of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulfur, such as ^{35}S .

Some isotopically-labelled compounds of the present invention, for example,
30 those, which include radioactive isotope, are used in studies of distribution of the pharmaceutical preparation and/or substrate in tissues. In particular, for this purpose, radioactive isotops are used, such as tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , considering that they are easy to administer, and their detection tools are available.

Substitution by more heavy isotops, such as deuterium, i.e. ^2H , may provide some
35 therapeutic effects conditioned by metabolical stability, for example, by an increase in the half-life period *in vivo* or a decrease in dosage limits, and, consequently, may be

preferable in some cases.

Isotopically-labelled compounds according to the invention may be obtained using general methods known to a skilled in the art, or by methods similar to those described in the attached examples of synthesis methods, when using appropriate isotopically-labelled reagents instead of unlabeled earlier used reagent.

Thus, this invention also refers to the use of compounds according to this invention for the diagnostics, including the distribution of the pharmaceutical preparation according to this invention or determination of targets, having affinity towards compounds of the present invention, in particular isotopically-labelled compounds according to this invention.

The term "wild type" used in the application specification means HIV virus strain, having dominant genotype present in normal population and resistant to the reverse transcriptase inhibitor. The term "wild type reverse transcriptase" used in the application specification means reverse transcriptase expressed by a wild type strain, which is sequenced and provided in SwissProt database under number P03366.

The term "reduced sensitivity" used in the application specification means an approximately 10-fold or more change in sensitivity of isolate of a specific virus strain or compared to the sensitivity, which is observed for a wild type virus under similar experimental conditions.

Compounds according to the present invention are obtained using methods shown in the schemes provided and described in section *Implementation of invention*. Starting materials and reagents, which are used in obtaining of the mentioned compounds, are commercial reagents supplied by firms, for example, Acros Organics, Alfa Aesar, Lancaster, Merck and Sigma-Aldrich, and others, or they are obtained using known methods according to procedures, described in literature, such as Fieser and Fieser, Reagents for Organic Synthesis, Wiley & Sons: New York, T.T. 1-21, R.C. LaRock, Comprehensive Organic Transformations, 2 ed., Wiley-VCH, New York (1999), Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.), T.T. 1-9 Pergamon, Oxford (1991), Comprehensive Geterocyclic Chemistry, A.R. Katritzky and C.W. Rees (Eds) Pergamon, Oxford, T.T. 1-9 (1984), Comprehensive Geterocyclic Chemistry II, A.R. Katritzky and C.W. Rees (Eds), Pergamon, Oxford, T.T. 1-11 (1986) and Organic Synthesis, Wiley & Sons: New York, T.T. 1-40 (1991), as well as provided in databases, such as SciFinder and Reaxis, but not limited to them. The following reaction schemes only illustrate some methods of synthesis of compounds according to this invention, and different modifications of these reaction schemes may be developed and proposed by a skilled in the art with a reference to materials of this application.

Starting materials and intermediate compounds in the mentioned reaction schemes may be obtained and, if necessary, purified using appropriate methods, including, with no limitation of those listed, filtration, distillation, crystallization, chromatography, etc. Such materials may be characterized by appropriate methods,
5 including physical constants and spectral data.

Unless otherwise stated, reactions provided in the application specification were preferably conducted in inert gas atmosphere at atmosphere pressure at the temperature of between approximately -78°C and approximately 150°C, more preferably between approximately 0°C and approximately 125°C, and the most preferably usually at room
10 temperature, for example, at approximately 20°C.

Some compounds in the shown schemes are provided with the inclusion of generalized substituents; however, it is quite obvious for a specialist that nature of groups R may vary according to the structure of different compounds according to this invention. Moreover, reaction conditions are typical, and alternative conditions are also well known.
15 It is assumed that the reaction sequence in the following examples does not limit the volume of the invention mentioned above in claims of the invention.

Pharmaceutically acceptable solvates according to the invention include solvates, where solvent may be isotopically substituted, for example, D₂O, d₆-acetone, d₆-DMSO.

The term “solvate” refers to an association or complex from one or several
20 molecules of the solvent and compounds according to the invention. Examples of solvents, forming solvates, include, but not limited to them, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid and ethanolamine.

The term “hydrate” refers to the complex, where solvent molecules are water.

Compounds of the present invention may exist in a free form or, if necessary, in
25 the form of pharmaceutically acceptable salts or other derivatives. The term **“pharmaceutically acceptable salt”** used herein refers to such salts, which, within the conducted medical conclusion, are suitable for the use in contact with human and animal tissues without excessive toxicity, irritation, allergic reaction, etc., and are consistent with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts of amines, carboxylic
30 acids, phosphonates and other types of compounds are well known in medicine. Salts may be obtained *in situ* in the process of isolation or purification of invention compounds, as well as may be obtained separately, by interaction of free acid or free base invention compounds with a suitable base or acid, respectively. Salt of amino groups formed by inorganic acids, such as hydrochloric, hydrobromic, phosphoric, sulfuric and chloric acids,
35 or by organic acids, such as acetic, oxalic, maleic, tartaric, succinic or malonic acids, or obtained by other methods used in this area, for example, with ion exchange, may be

examples of pharmaceutically acceptable, non-toxic acid salts. Other pharmaceutically acceptable salts are as follows: adipate, alginate, ascorbate, aspartate, benzene sulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphor sulfonate, citrate, cyclopentanepropionate, digluconate, dodecyl sulfate, ethane sulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalene sulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate and similar. Typical salts of alkaline and alkali-earth metals contain sodium, lithium, potassium, calcium, magnesium, etc. Moreover, pharmaceutically acceptable salts may contain, if necessary, nontoxic cations of ammonium, quaternary ammonium and amine, obtained using counterions, such as halogenides, hydroxides, carboxylates, sulfates, phosphates, nitrates, lower alkyl sulfates and aryl sulfonates.

Compounds of the present invention may exist in the form of pharmaceutically acceptable esters. The term "pharmaceutically acceptable esters" refers to derivatives of compounds of the present invention, wherein carboxyl group is converted to ester. Lower alkyl, lower hydroxyalkyl, lower-alkoxy-lower-alkyl, amino-lower-alkyl, mono- or di-lower-alkyl-amino-lower-alkyl, morpholine-lower-alkyl, pyrrolidine-lower-alkyl, piperidine-lower-alkyl, piperazine-lower-alkyl, lower-alkyl-piperazine-lower-alkyl and arylalkyl esters are examples of suitable esters. Specific esters are as follows: methyl, ethyl, propyl, butyl and benzyl esters. Moreover, the term "pharmaceutically acceptable esters" covers compounds of the present invention, wherein hydroxy groups are converted into respective esters by organic or inorganic acids, such as nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and similar, which are non-toxic for living organisms.

If one of the starting materials or compounds of the present invention contains one or more functional groups, which are not stable or are reactive under the reaction conditions of one or several reaction stages, respective protection groups (as described, for example, in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wuts, 3rd Ed., 1999, Wiley, New York) may be introduced before the critical stage using methods well known in this area. Such protective groups may be eliminated at the later stage of the synthesis using standard methods described in literature. Examples of protective groups are as follows: tert-butoxycarbonyl (Boc), 9-fluorenylmethyl carbamate

(Fmoc), 2-trimethylsilylethyl carbamate (Teoc), carbobenzyloxy (Cbz) and p-methoxybenzyloxycarbonyl (Moz).

Compound of the present invention may contain several asymmetrical centers and may be present in the form of optically pure enantiomers, enantiomer mixtures, such as, for example, racemates, diastereoisomer mixtures, diastereoisomer racemates or diastereoisomer racemate mixtures.

"Asymmetric carbon atom" is defined as carbon atom with four different substituents. According to Cahn-Ingold-Prelog rules, asymmetric carbon atom may be of *R*- or *S*-configuration.

Another embodiment of the present invention relates to pharmaceutical compositions or pharmaceutical preparations, containing compounds for the invention and therapeutically inert carrier, diluent or excipient, as well as methods for use of compounds according to the invention to obtain such compositions and pharmaceutical preparations. In one variant, compounds of the present invention may be prepared by stirring at room temperature, corresponding pH and at a desirable grade, with physiologically acceptable carriers, for example, carriers, which are non-toxic for recipients in doses and concentrations used, in galenic formulation. Specific use and concentration of compound mostly affect the pH of the composition, but preferably it may vary in the range of about 3 to about 8. In another embodiment, compounds of the present invention are sterile. Compound may be stored, for example, in a solid or amorphous composition, in the form of lyophilized preparation or in the form of water solution.

Compositions are prepared, dosed and administered according to good medical practice. Factors considered in this context include a specific disorder to be managed, specific mammal to be treated, clinical condition of specific patient, cause of the disorder, agent site of delivery, method of administration, dosage regimen and other factors familiar to clinicians.

Compounds according to the invention can be administered by any appropriate route, including orally, locally (including transbuccally and sublingually), rectally, vaginally, transdermally, parenterally, subcutaneously, intraperitoneally, intrapulmonary, intradermally, intrathecally, epidurally and intranasally. Parenteral infusions include intramuscular, intravenous, intra-arterial, intraperitoneal or subcutaneous administration.

Compounds according to this invention can be administered in any suitable pharmaceutical form, for example, tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain general for pharmaceutical preparations ingredients, for example, diluents, carries, pH modifiers, sweeteners, excipients and other active

ingredients.

Typical preparation is obtained by mixing the compound for the present invention and carrier or excipient. Acceptable carriers and excipients are well known to specialists in the field of the present invention and are well described, for example, in Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. Compositions may also include one or more buffers, stabilizing agents, superficially active substances, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing additives, colorants, sweeteners, flavourings, fragrances, diluents and other known additives, providing elegant presentation of the product (for example, compounds according to this invention or its pharmaceutical composition) or helping in the manufacture of the pharmaceutical product (for example, pharmaceutical preparation).

Thus, this invention also refers to:

Compound of the present invention for the use as therapeutically active substance;

Compound of the present invention for the use as reverse transcriptase inhibitor;

Compound of the present invention for the use as a pharmaceutical preparation, having anti-HIV antiviral activity;

Pharmaceutical composition, containing a compound according to the present invention and therapeutically inert carrier;

Use of compounds according to the present invention for the treatment or prevention of HIV;

Pharmaceutical composition, having activity towards HIV reverse transcriptase, including a compound according to this invention in a therapeutically effective amount, and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors;

Use of compounds according to this invention for obtaining a pharmaceutical preparation for the treatment or prevention of HIV;

Compound of the present invention for the treatment or prevention of HIV; and

Method for the treatment or prevention of HIV, which includes administration of an effective amount of compounds of the present invention to a patient in need thereof.

Modification of compounds for the invention for raising their solubility in water or

other carrier is reached by using simple enough techniques (obtaining of salts, etherification, etc.), which are well known to skilled in the art. Moreover, a specialist may change the route of administration and the treatment course with a specific compound to regulate pharmacokinetics of compounds for the invention and to achieve maximum therapeutic effect for the patient.

The term "therapeutically effective amount" used in the application description means an amount necessary to decrease the intensity of disease symptoms in a patient. The level of the development of HIV infection is established by measuring viral load (RNA) or T-cells level. The dose may be adjusted according to individual requirements in each particular case. The dose may be adjusted in a wide range depending on many factors, such as, severity of the disease being managed, age and relative health condition of the subject, use of other pharmaceutical preparations by the patient, route of administration and dosage form, experience and qualification of the physician. In case of oral administration, suitable daily dose is between approximately 0.01 and approximately 100 mg/kg of body weight, when treated with one pharmaceutical preparation and/or in combination therapy. Preferable daily dose is between approximately 0.1 and approximately 500 mg/kg of body weight, more preferably between 0.1 and 100 mg/kg of body weight and more preferably between 1.0 and approximately 10 mg/kg body weight. Thus, for administering to the patient with a body weight of 70 kg, the dose is between approximately 7 mg and approximately 0.7 g per day. Daily dose may be administered as a single dose or as 1-5 divided doses. Usually, the treatment is started with administration of doses, not exceeding the optimal dose. Then, the dose is gradually increased to achieve optimal action for a particular patient. A specialist in the mentioned diseases without any experiments, based on his/her own experience and specification of the present invention, may determine a therapeutically effective number of compounds according to this invention necessary to manage this disease in a particular patient.

Active compound for the invention or its salt may be administered in combination with other antiviral agent, such as nucleoside reverse transcriptase inhibitor or HIV protease inhibitor. In case of administration of an active compound or its derivative or salts in combination with another antiviral agent, activity of the combination may exceed the activity of initial compounds. In case of combination therapy, such an administration may be conducted simultaneously with or sequentially with administration of nucleosides derivatives. Consequently, the term "simultaneous administration" used in the application specification includes administration of agents simultaneously or at different times. Two or more agents may be administered simultaneously as part of one formulation, containing two or more active ingredients; or two or more formulations, each containing

one active ingredient, may be administered almost simultaneously.

It is assumed that references to treatment include prevention, as well as treatment of conditions observed. Moreover, the term "treatment of HIV infection" used in the application specification also includes treatment or prevention of the disease or condition associated or mediated by HIV infection, or its clinical symptoms.

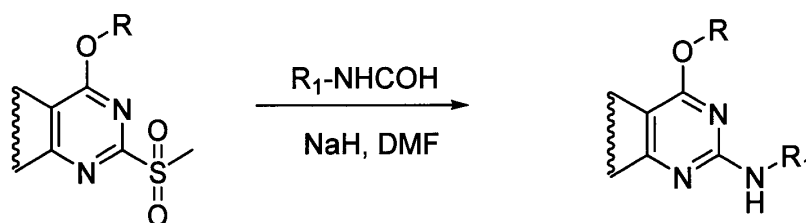
Pharmaceutical preparations preferably represent standard pharmaceutical forms. In such a form, the product is divided into standard doses, containing appropriate amounts of the active ingredient. A standard pharmaceutical form may be a packed product, moreover, the packaging contains discrete amounts of the product, such as, packed tablets, capsules, and powders in bottles or ampules. Moreover, a standard dose may be a capsule, tablet, starch capsule or cake, or may be a packaging, containing a specific amount of any of the specified dosage forms.

Best Mode for Carrying Out the Invention

The invention is illustrated by the following examples, not limiting their volume. The examples and products mentioned below are provided with a purpose of explaining the summary of the invention and supporting its practical use.

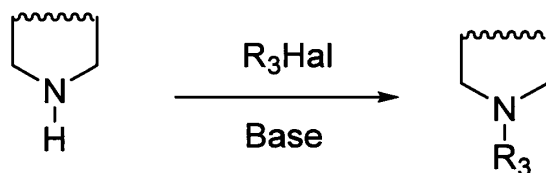
EXAMPLES

General procedure for substitution of sulfogroups by the activated amine (Reaction XIX)

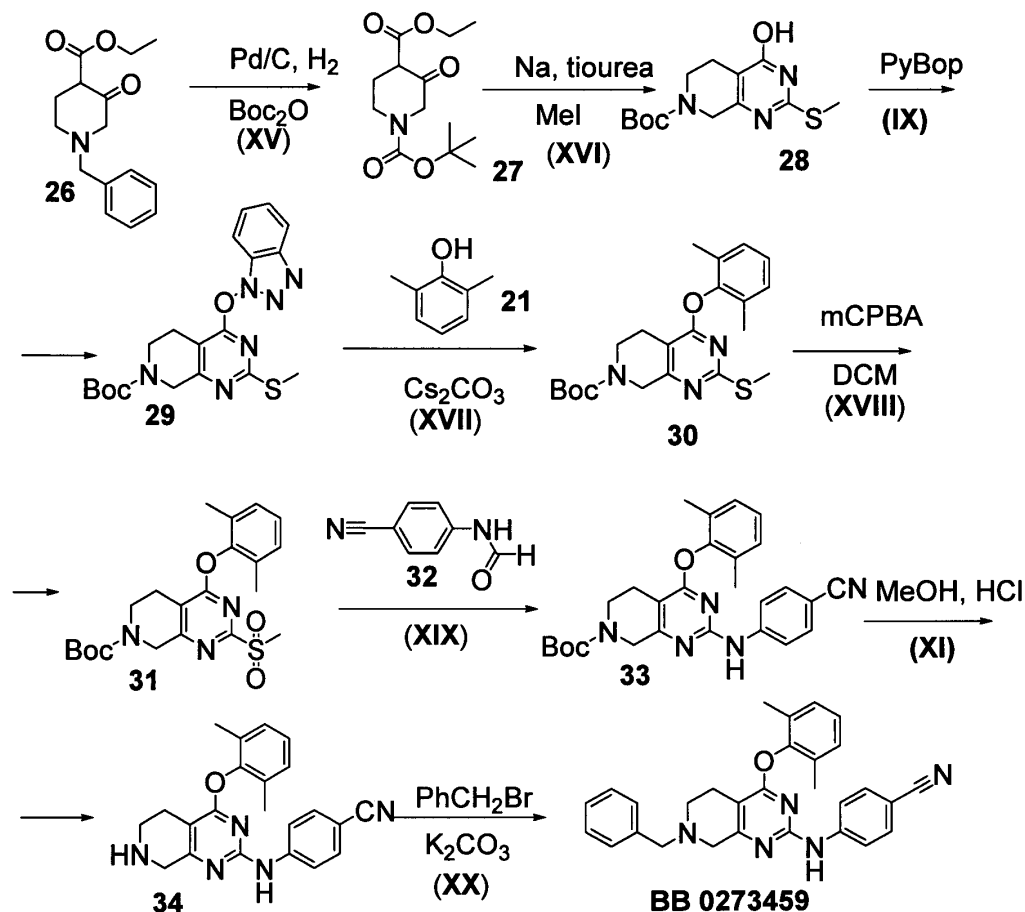


Add NaH (7 mmol, 1.8 eq.) to the formamide solution (3.9 mmol, 1 eq.) in dimethylformamide (15 ml) at the temperature of 0°C. Mix the reaction mixture at room temperature for 20 minutes. Then again cool the mixture to 0°C and add sulfone to it (3.9 mmol, 1.0 eq.). Mix the reaction mixture for 8 hours, then boil out organic solvent, add water to the residue (pH=9). Filter the residue formed and wash with water. Dissolve the residue in methylene chloride and conduct purification by chromatography using Hex:EA (1:1) as eluent.

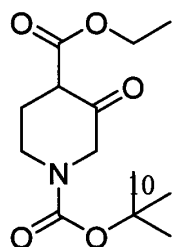
General procedure for alkylation of substituted tetrahydropyrimidines derivatives

(Reaction XX)

- Transfer pyrimidine in the form of a free base (1 mmol, 1 eq.) and alkylbromide (1.1 mmol) into a 50 ml round-bottomed flask equipped with an effective reflux condenser with a chlorocalcium tube. Boil the mixture, until all the mass is solidified. Hydrobromide of the target product is formed. At the end of reaction, cool the flask and pour in portions (while cooling to avoid significant heating) 1 g caustic soda solution into 20 ml of water. Determine the extracted product in a separation funnel, add chlorous, wash the organic phase with water, dry over anhydrous sodium sulfate. Remove the organic solvent at underpressure, and purify the residue by chromatography using Hex:EA (1:3) as eluent.

Example 1.**Synthesis of 4-((7-benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)benzonitrile**

5

1-(Tert-butyl) 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (27)

Dissolve hydrochloride **26** (59.6 g, 0.2 mole, 1 eq.) in ethanol (400 ml) and add triethylamine (27.8 ml, 0.2 mole, 1 eq.), mix for 5 minutes. Then add 5% Pd/C (5 g) to the reaction mass. Degas the reaction mixture and conduct the reaction of debenzylation in hydrogen environment. Stir the reaction mixture for 3 days, then add Boc₂O (43.6 g, 0.2 mole, 1 eq.). Stir the reaction mixture for three hours, then pass through a layer of silit, add cold water (250 ml) and dichloromethane (500 ml). Separate the organic layer, wash twice with water (2 x 150 ml), dry over anhydrous sodium sulfate, filter the drying agent, and remove the organic solvent on a rotary evaporator at underpressure. Purify the residue by column chromatography using Hex:EA (3:1) as

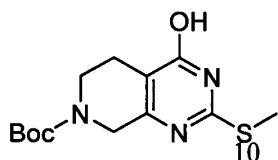
15

eluent. Rf = 0.6.

Weight = 20 g

Yield = 52%

5 ***Tert-butyl* 4-hydroxy-2-(methylthio)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (28)**

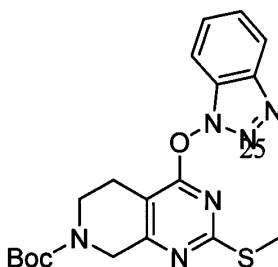


To sodium ethoxide solution obtained by dissolution of Na (1.95 g, 81 mmol, 3.0 eq.) in absolute ethanol (100 ml), add thiourea (3.22 g, 42 mmol, 1.5 eq.) and ketoester (27) (7.67 g, 28.2 mmol, 1.0 eq.). The reaction mixture was boiled for 8 hours, then the mixture was cooled to the room temperature and added to it dropwise from a dropping funnel while stirring MeI (1.76 ml, 28.2 mmol, 1 eq.). After adding of alkylating reagent, the mixture was mixed at the room temperature for 1 hour. The reaction mixture was boiled, the residue was dissolved in water. During acidification of water solution with citric acid to pH 3-4, precipitation occurred, which was filtered, washed sequentially with water, hexane, ethylacetate, ester.

Weight = 7.8 g

Yield = 85%

20 ***Tert-butyl* 4-((1H-benzo[d][1,2,3]triazole-1-yl)oxy)-2-(methylthio)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (29)**

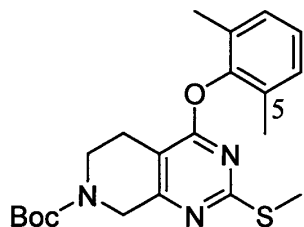


Dissolve pyrimidine 28 (5.68 g, 19.1 mmol, 1 eq.) in 80 ml of dimethylformamide, then add triethylamine (TEA) (2.66 ml, 19.1 mmol, 1 eq.) and, in 5 minutes, add benzotriazole-1-yl-oxytripyrrolidinephosphonium hexafluorophosphate (PyBop) (9.9 g, 19.1 mmol, 1 eq.). Stir the reaction mixture for 5 hours, then pour into ethylacetate, and wash the organic phase with sodium hydrocarbonate saturated solution. Boil out the organic layer and purify by column chromatography using Hex:EA (3:1) as eluent.

Weight = 4.6 g

Yield = 68%.

***Tert-butyl* 4-(4-cyano-2,6-dimethylphenoxy)-2-(methylthio)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (30)**

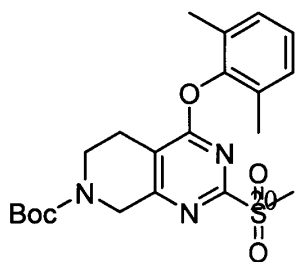


Dissolve pyrimidine **29** (4.1 g, 8.5 mmol, 1 eq.) in dimethylformamide (50 ml), then add phenol **21** (1.24 g, 8.5 mmol, 1 eq.) and cesium carbonate (2.76 g, 8.5 mmol, 1 eq.). Mix the reaction mixture for 8 hours, then pour into ethylacetate and wash with water. Boil out the organic layer and purify by column chromatography using Hex:EA (3:1) as

eluent.

- 10 Weight = 3.2 g
 Yield = 85%.
 LCMS (M+H) = 402

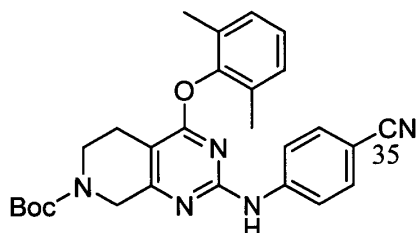
***Tert-butyl* 4-(4-cyano-2,6-dimethylphenoxy)-2-(methylsulfonyl)- 5,8-dihydro-pyrido[3,4-d]pyrimidine-7(6H)-carboxylate (31)**



To pyrimidine **30** (3.0 g, 7 mmol, 1 eq.) solution in dichloromethane (50 ml) at 0°C, add m-chloroperbenzoic acid (mCPBA) (3.8 g, 21.1 mmol, 3 eq.). Stir the reaction mixture for 24 hours. Then to stop the reaction, add to the mixture saturated water solution of NaHCO₃. Extract the obtained product with dichloromethane. Boil out the organic phase on a rotary evaporator and purify by column chromatography using Hex:EA (1:1) as eluent.

- Weight = 2.2 g
 Yield = 54%
- 25 ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.46 (s, 9 H), 2.11 (s, 6 H), 2.98 (t, J=5.4 Hz, 2 H), 3.12 (s, 3 H), 3.76 (t, J=5.5 Hz, 2 H), 4.72 (broadened singlet, 2 H), 7.72-7.78 (m, 3 H)
- LCMS (M+H) = 434

***Tert-butyl* 2-((4-cyanophenyl)amino)-4-(2,6-dimethylphenoxy)-5,8-dihydropyrido[3,4-d]pyrimidine-7(6H)-carboxylate (32)**

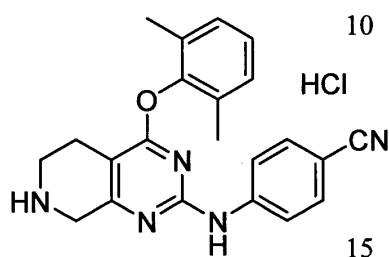


To formamide **32** (0.51 g, 3.9 mmol, 1 eq.) solution in dimethylformamide (15 ml), add NaH (0.28 g, 7 mmol, 1.8 eq.) at the temperature of 0°C. Stir the reaction mixture at the room temperature for 20 minutes. Then cool down the mixture to 0°C

again and add sulfone **31** (1.8 g, 3.9 mmol, 1.0 eq.) to it. Stir the reaction mixture for 8 hours, then boil out the organic solvent, add water to the residue (pH=9). Filter the obtained residue and wash with water. Dissolve the residue in dichloromethane and purify by chromatography using Hex:EA (1:1) as eluent.

5 Weight = 520 mg
 Yield = 42%

4-(((4-(2,6-Dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)-benzonitrile hydrochloride (33**))**

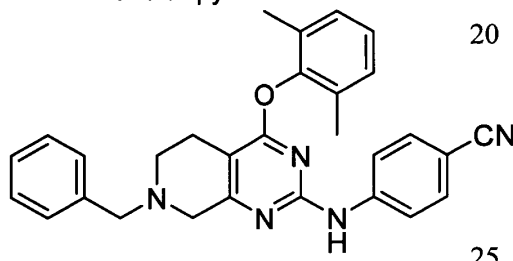


Dissolve pyrimidine **32** (500 mg) in methanole saturated with hydrogen chloride, mix for an hour, boil out the organic solvent, recrystallize the precipitate formed from ethanol.

Weight = 500 mg
Yield = 96%

4-(((7-Benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)methyl)benzonitrile (BB 0273459)

Transfer pyrimidine **20** in the form of a free base (500 mg, 1 mmol, 1 eq.) and



benzylbromide (205.5 mg, 1.1 mmol) into a 100 ml round-bottomed flask equipped with an effective reflux condenser with a calcium chloride tube. Boil the mixture, until all the mass is solidified.

Hydrobromide of target N-benzyl pyrimidine is formed. At the end of reaction, cool the flask and pour in portions (while cooling to avoid significant heating) 1 g caustic soda in 20 ml of water solution. Separate the product extracted in a separation funnel, add chlorous, wash the organic phase with water, dry over anhydrous sodium sulfate. Remove the organic solvent at underpressure, purify the residue by chromatography, using Hex:EA (1:3) as eluent.

Weight = 300 mg
Yield = 58%

BB 0273459

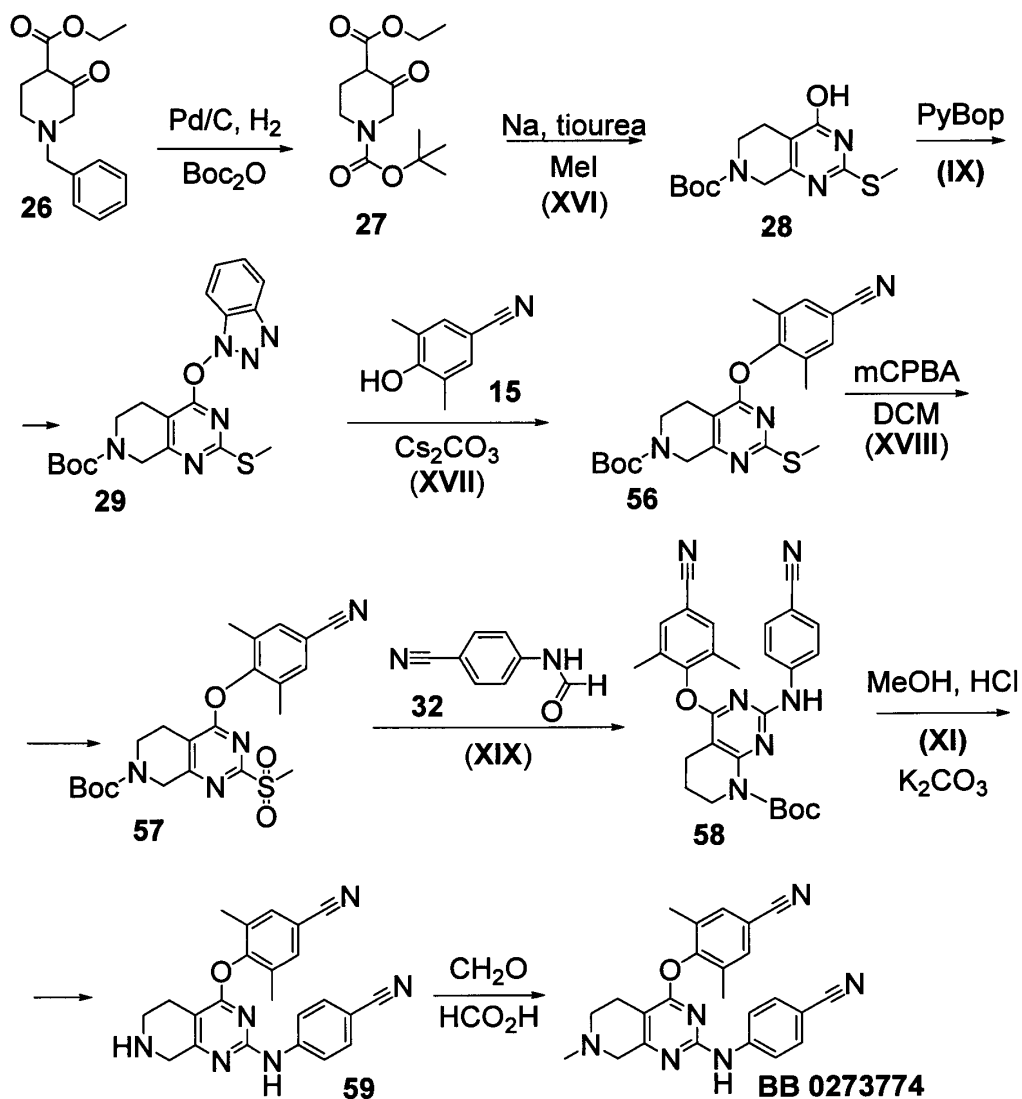
1H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.95 - 2.13 (m, 6 H), 2.78 (broadened singlet, 2 H), 3.43 (broadened singlet, 2 H), 3.47 - 3.57 (m, 2 H), 3.64 - 3.79 (m, 2 H),

7.19 - 7.46 (m, 12 H)

LCMS $m/z(M+H)$: 462.**Example 2.**

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile

5

**BB 0273774**

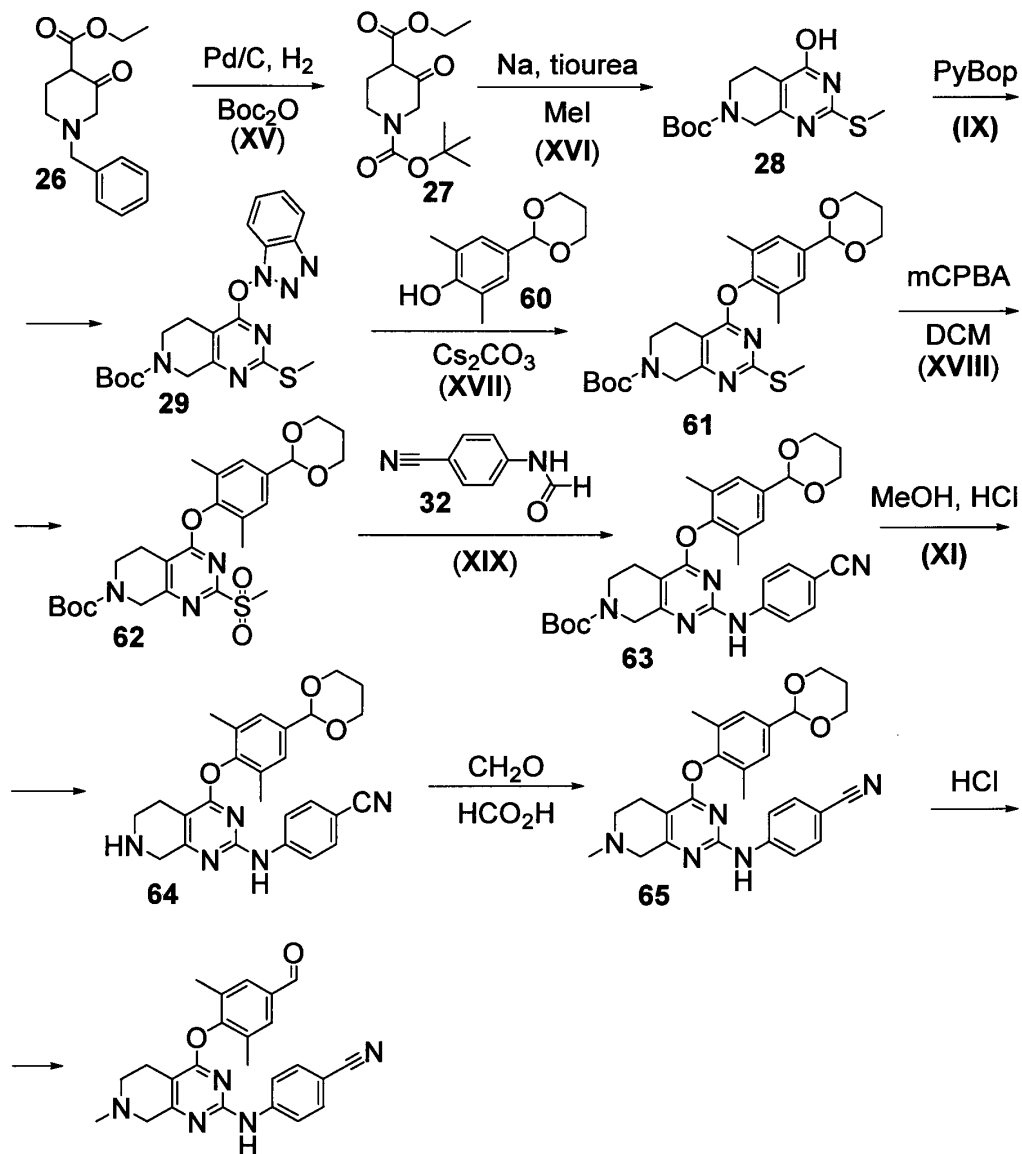
^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.26 (s, 3H), 2.18 (s, 6H), 2.20-2.22 (m, 2H), 3.12 – 3.15 (m, 2H), 7.22 (d, $J=8.2$ Hz, 2H), 7.35 (d, $J=8.4$ Hz, 2H), 7.55 (s, 2 H).

Weight Yield - 4.5 mg (8%)

LCMS m/z (M+H): 411.

Example 3.

Synthesis of 4-((4-(4-Formyl-2,6-dimethylphenoxy)-7-methyl-5,6,7,8-tetrahydro[3,4-d]pyrimidine-2-yl)amino)benzonitrile



5

BB 0273775**BB 0273775** $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ , ppm): 1.26 (s, 3H), 2.18-2.20 (m, 2H), 2.23 (s, 6H),

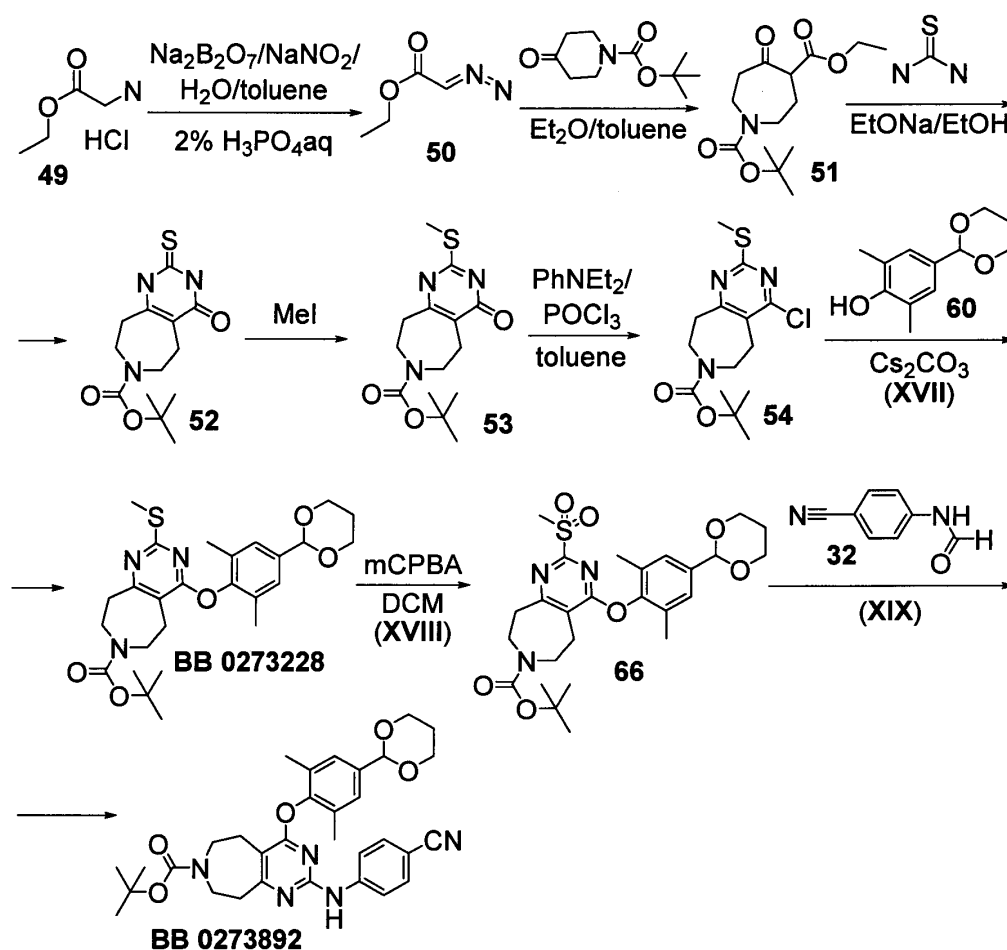
3.14 – 3.18 (m, 2H), 3.74 – 3.78 (m, 2H), 7.20 (d, $J=8.4$ Hz, 2H), 7.28 (d, $J=8.4$ Hz, 2H), 7.76 (s, 2 H), 10.07 (s, 1 H).

Weight Yield - 8.2 mg (12%)

LCMS m/z (M+H): 413

Example 4.

5 **Synthesis of *tert*-butyl 4-(4-(1,3-dioxolane-2-yl)-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate**



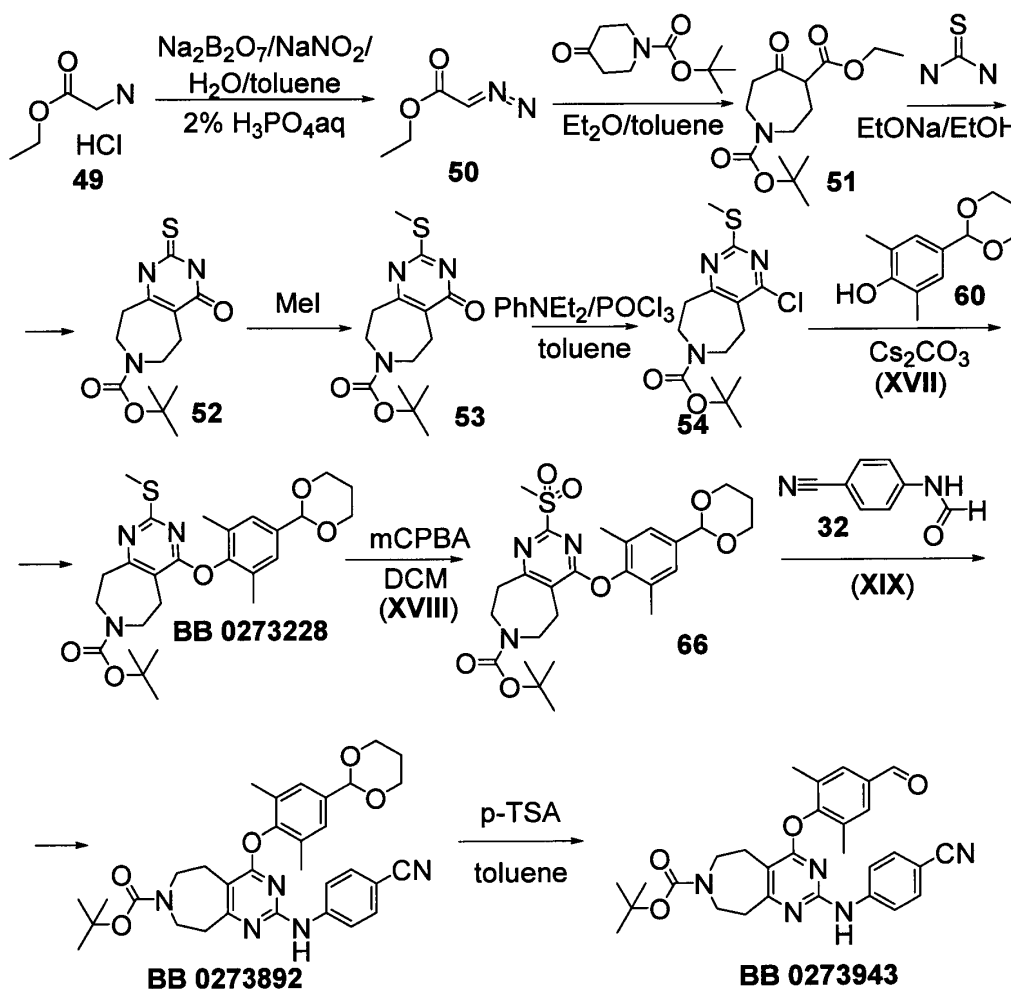
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BB 0273892

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.51 (s, 10H), 2.09 (s, 6H), 2.20-2.42 (m, 1H), 2.94-3.18 (m, 4H), 3.66 (broadened singlet, 4H), 4.06 (t, $J=12.3$ Hz, 2H), 4.36 (dd., $J=10.97$ Hz, 4.86 Hz, 2H), 5.55 (s, 1H), 7.08 (s, 1H), 7.16 (d, $J=8.56$ Hz, 2H), 7.30 (s, 2H), 7.41 (d, $J=8.74$ Hz, 2H),

Weight Yield - 0.0043 g (12%)

LCMS m/z (M+H): 572.

Example 5.**Synthesis of *tert*-butyl 2-((4-cyanophenyl)amino)-4-(4-formyl-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate****BB 0273943**

¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.51 (s, 9H), 2.19 (s, 6H), 3.09 (broadened singlet, 4H), 3.68 (broadened singlet, 4H), 7.12 (broadened singlet, 1H), 7.30 (s, 4H), 7.70 (s, 2H), 10.02 (s, 1H).

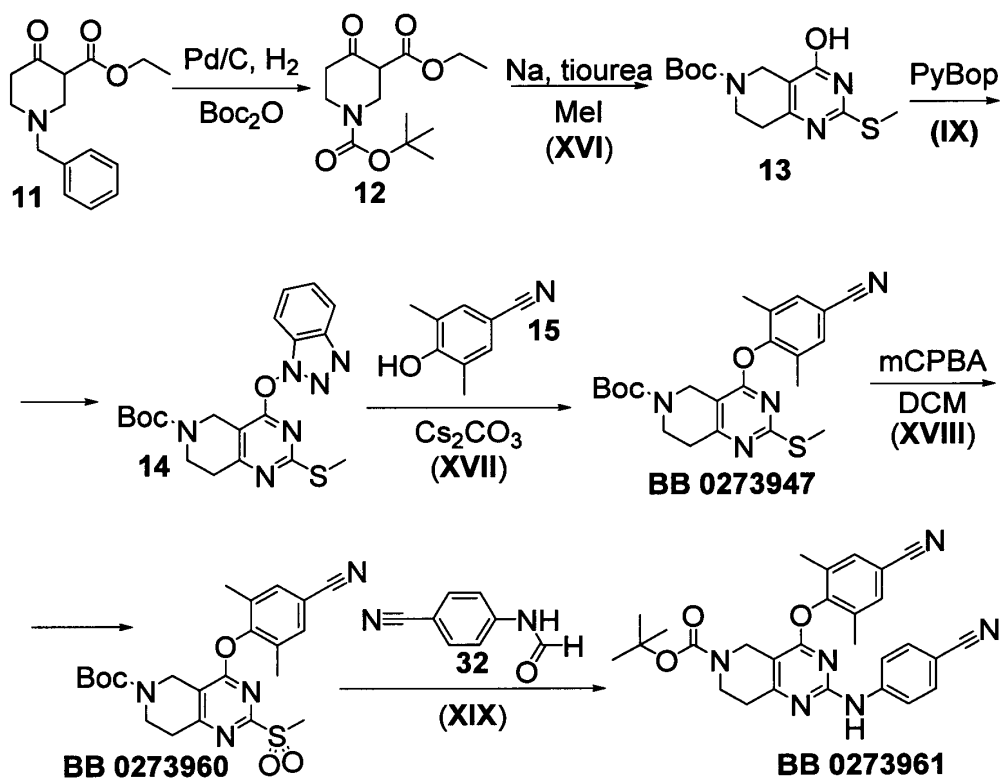
Weight Yield - 0.056 g (12%)

LCMS m/z (M+H): 514.

Example 6.

Synthesis of *tert*-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

5

**BB 0273961**

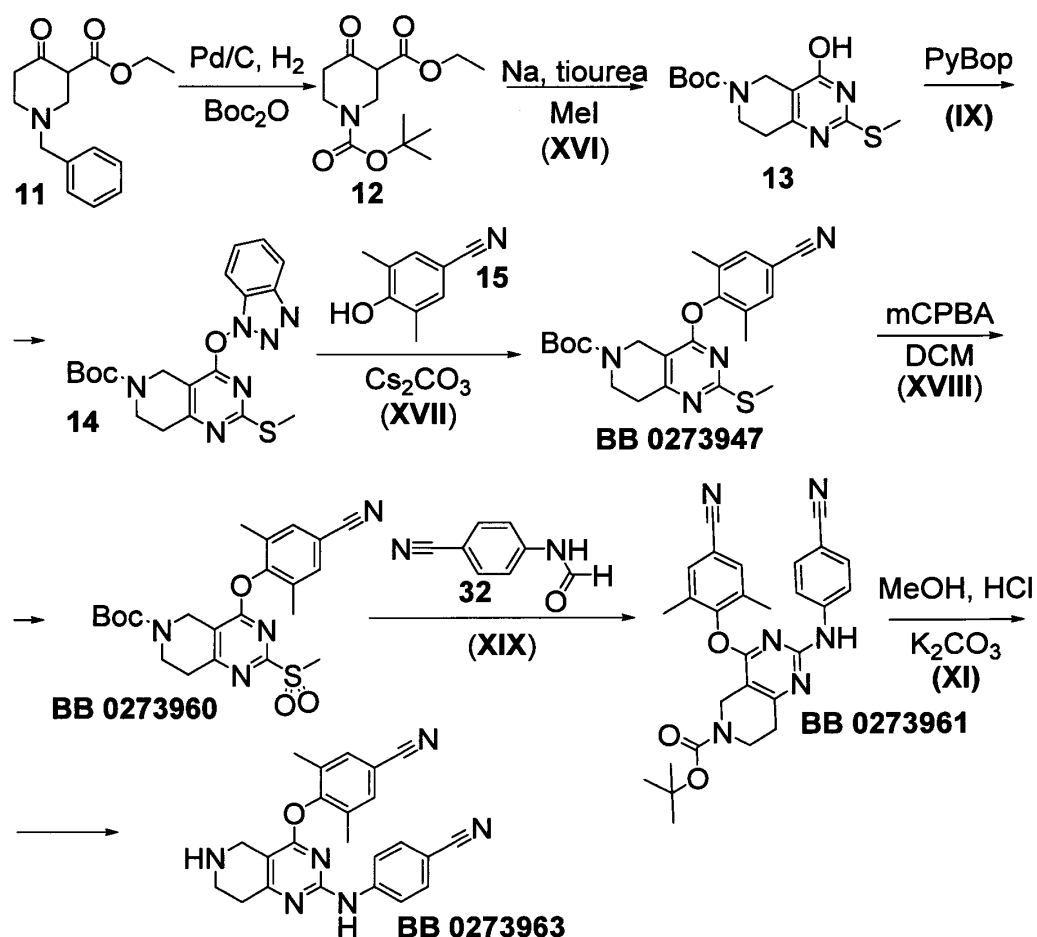
^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.53 (s, 9H), 2.16 (s, 6H), 2.82 - 2.89 (m, 2 H), 3.81 (t, $J=5.6$ Hz, 2 H), 4.62 (broadened singlet, 2H), 7.39 (d, $J=8.8$ Hz, 4H), 7.48 (s, 2H).

Weight Yield - 2.87 g (46%)

LCMS m/z (M+H): 497.

Example 7.

Synthesis of 4-((2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0273963

^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.11 (s, 6H), 3.02 (t, $J=5.8$ Hz, 2 H), 3.50 (d, $J=5.2$ Hz, 2H), 4.31 (broadened singlet, 2H), 7.47 (broadened singlet, 4 H), 7.79 (s, 2 H).

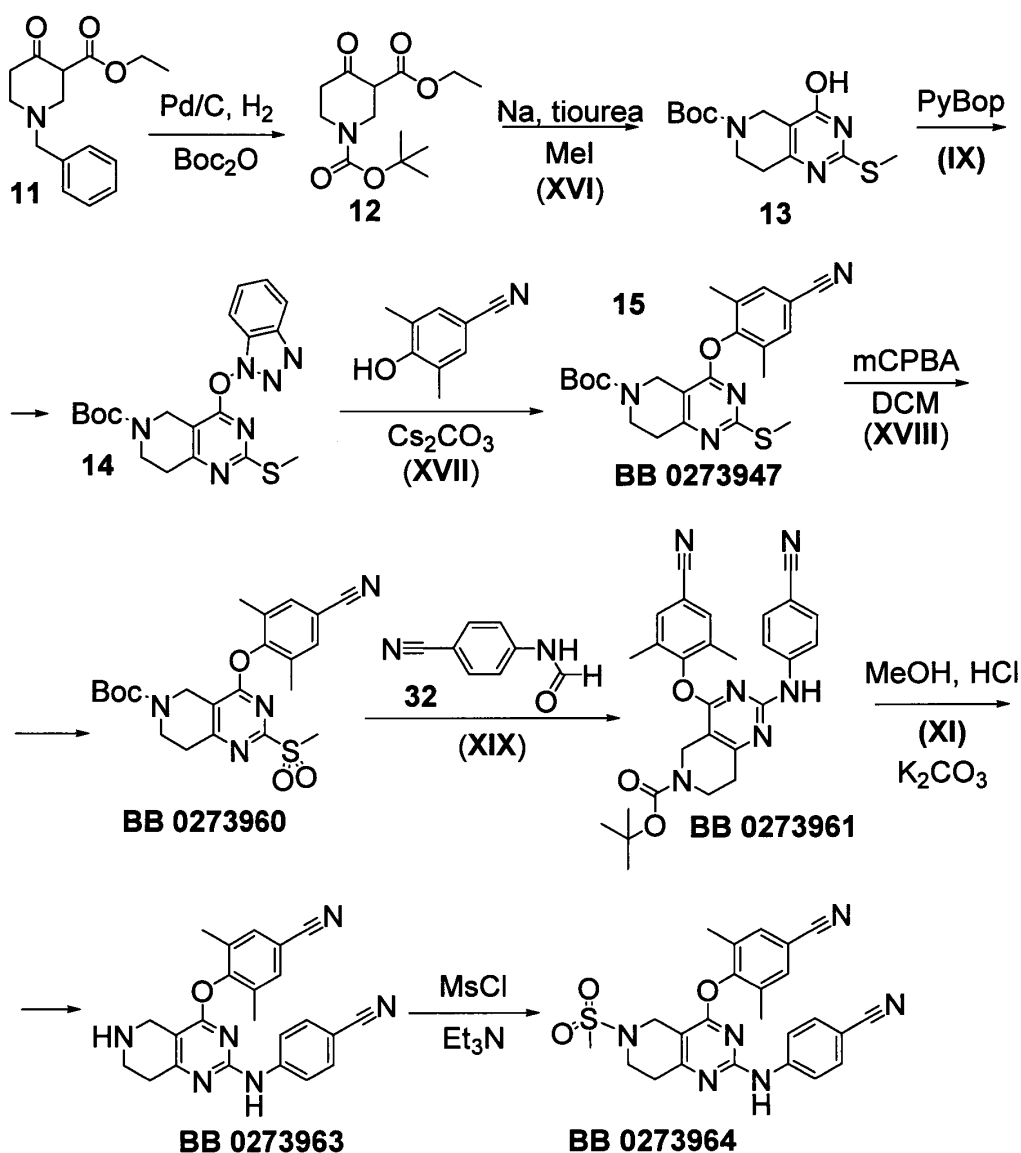
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Weight Yield - 2.08 g (96%)

LCMS m/z (M+H): 397.

Example 8.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0273964

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.16 (s, 6H), 2.98 (s, 3H), 3.04 (t, $J=5.8$ Hz, 2H), 3.67 - 3.72 (m, 2H), 4.50 (s, 2H), 7.34 - 7.40 (m, 2H), 7.41 - 7.45 (m, 2H), 7.49 (s, 2H)

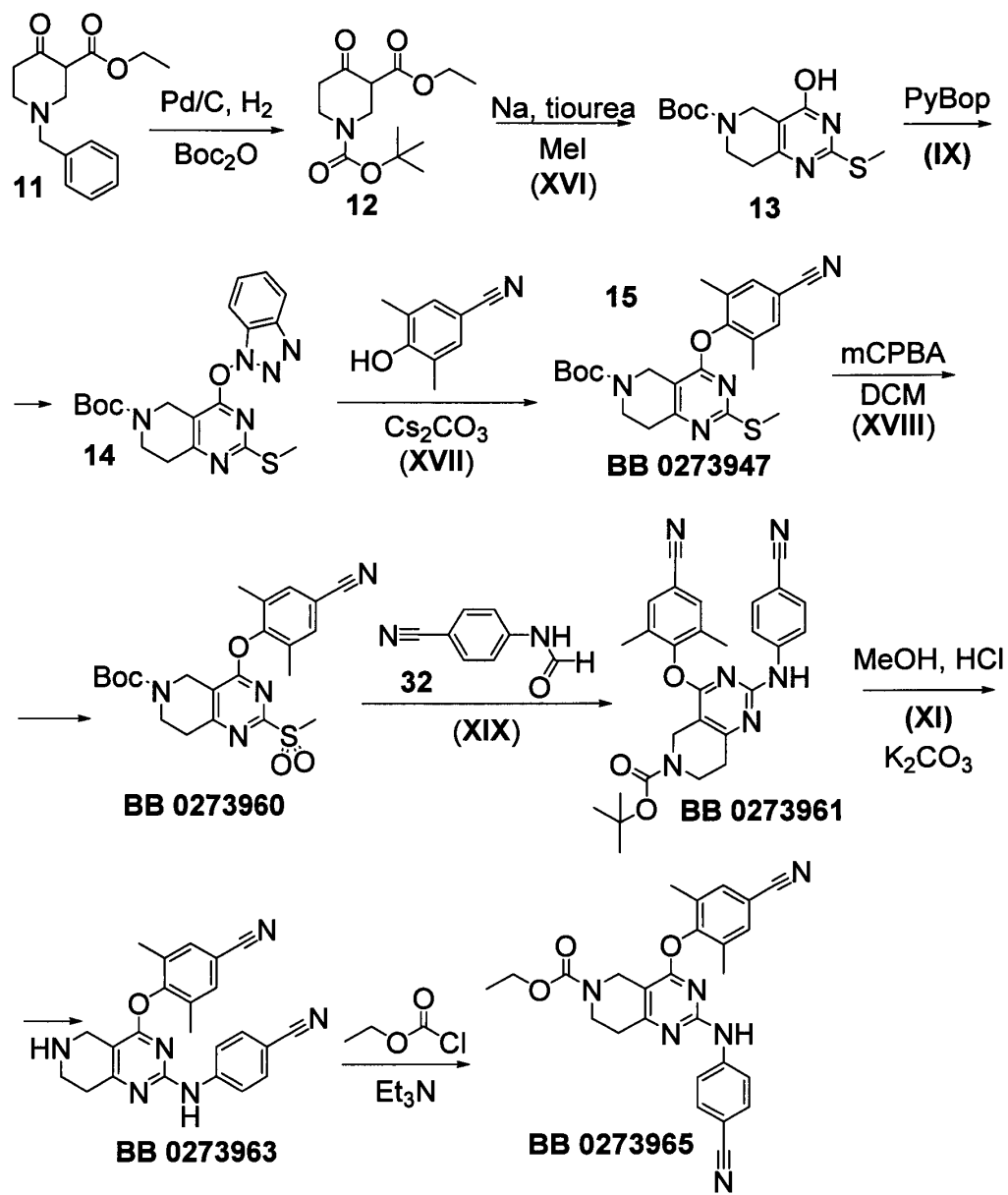
Weight Yield - 0.072 g (84%)

10

LCMS m/z ($M+H$): 475.

Example 9.

Synthesis of ethyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate



BB 0273965

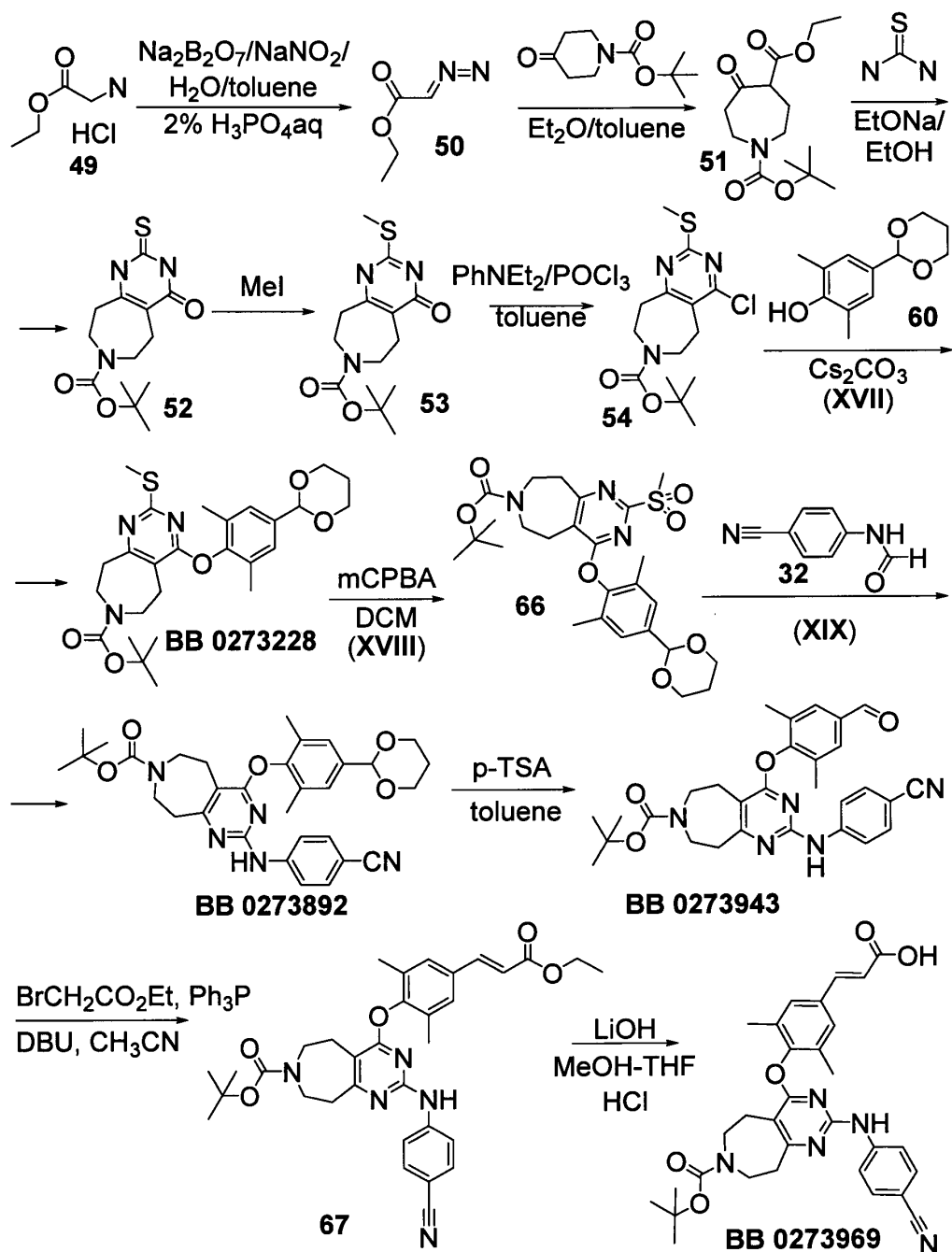
5 ^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.33 (t, $J=7.1$ Hz, 3H), 2.17 (s, 6 H), 2.89 (t, $J=5.5$ Hz, 2H), 3.86 (t, $J=5.7$ Hz, 2H), 4.24 (kv., $J=7.1$ Hz, 2H), 4.67 (s, 2 H), 7.39 (d, $J=8.9$ Hz, 4H), 7.49 (s, 2 H)

Weight Yield - 0.056 g (56%)

LCMS m/z (M+H): 468.

Example 10.

Synthesis of (E)-3-(4-((7-(*tert*-butoxycarbonyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylphenyl)acrylic acid

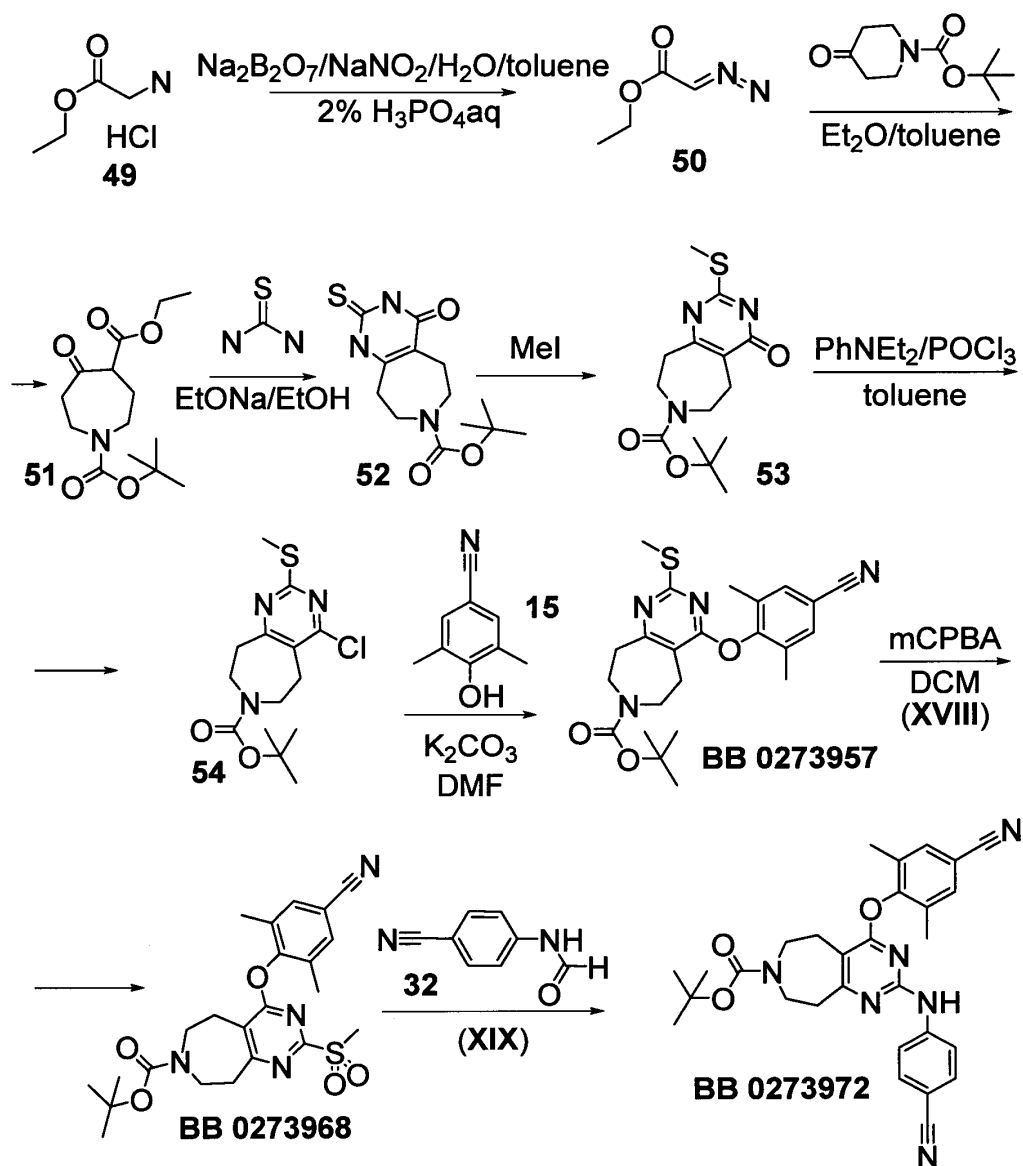


BB 0273969

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.40 (broadened singlet, 9H), 2.07 (s, 6H), 3.02 (broadened singlet, 4H), 3.59 (broadened singlet, 4H), 6.56 (d, *J*=16.0 Hz, 1H), 7.27-7.39 (m, 2H), 7.40-7.52 (m, 2H), 7.53-7.67 (m, 2H), 9.95-10.09 (m, 1H).

Example 11.

Synthesis of *tert*-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate



BB 0273972

¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.51 (s, 9H), 2.14 (s, 6H), 3.06 – 3.10 (m, 4H), 3.65 – 3.68 (m, 4H), 7.07 (broadened singlet, 1H), 7.29-7.35 (m, 2H), 7.36-7.42 (m, 2H), 7.48 (s, 2H),

Weight Yield - 0.462 g (24%)

LCMS m/z (M+H): 511.

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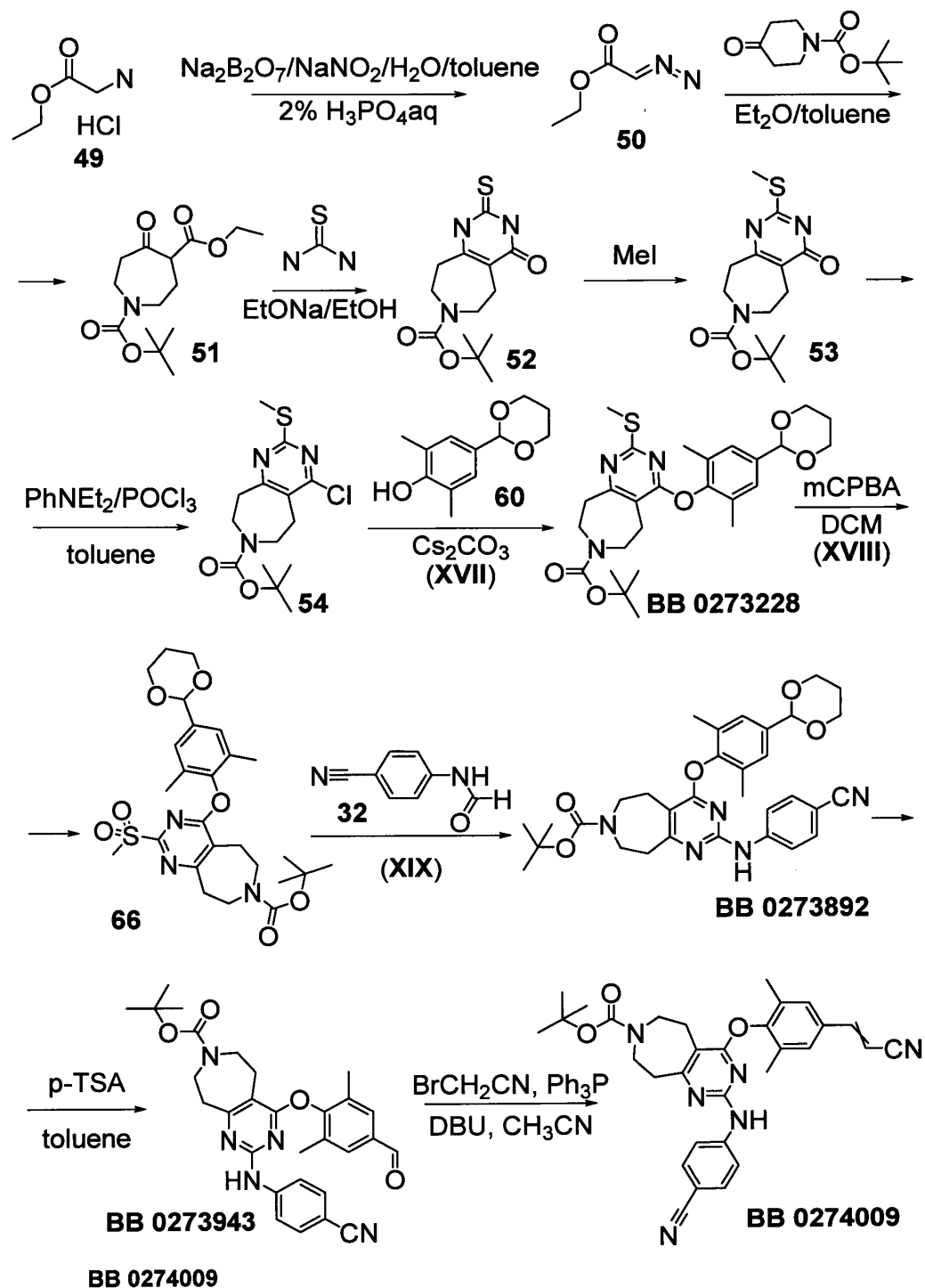
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Synthesis of tert-butyl 2-((4-cyanophenyl)amino)-4-(4-(2-cyanovinyl)-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate



- 5 ^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.51 (s, 9H), 2.10-2.17 (m, 6H), 3.08 (broadened singlet, 4H), 3.67 (broadened singlet, 4H), 5.90-5.46 (m, 1H), 7.63-7.04 (m, 8H),

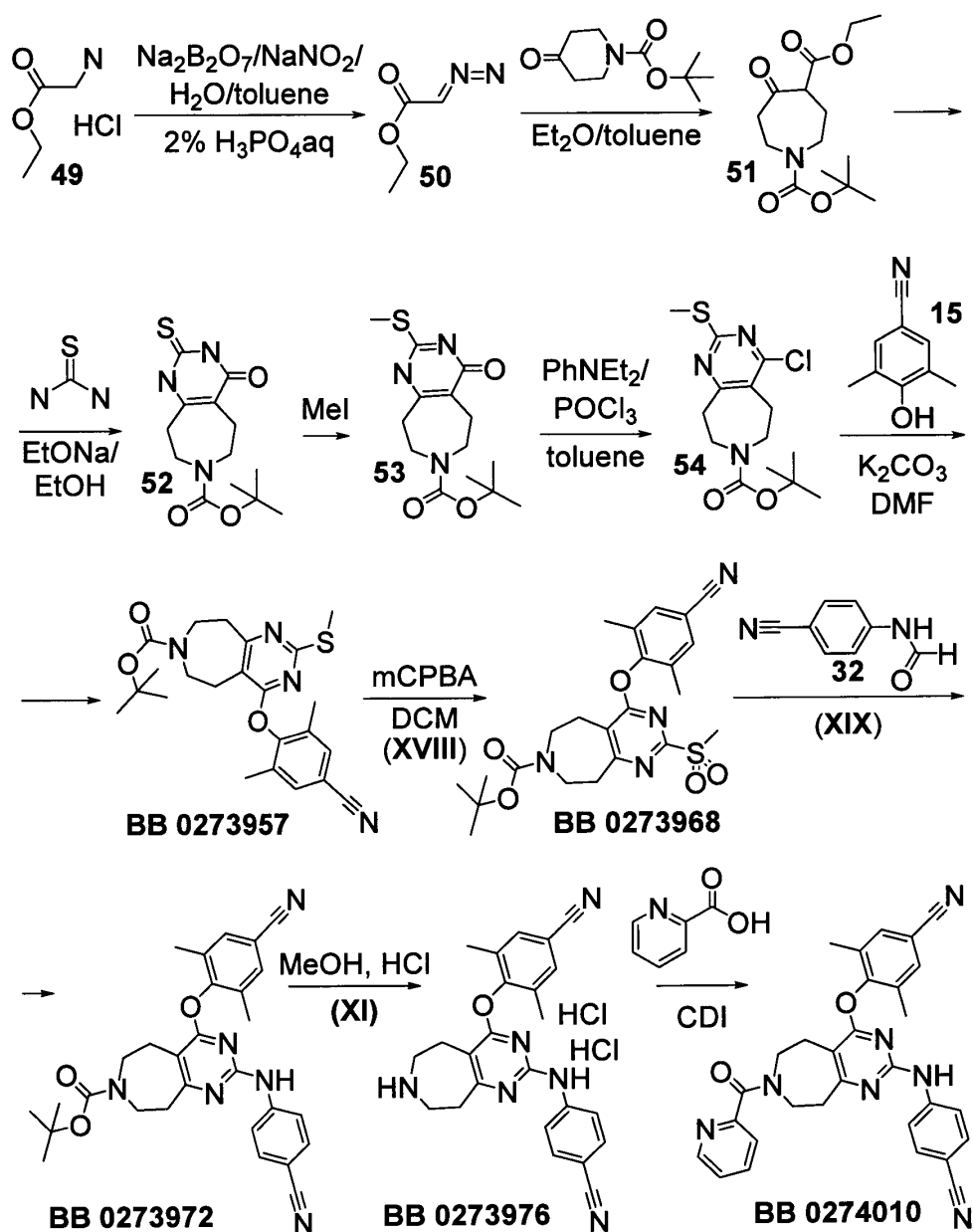
Weight Yield - 0.06 g (8%)

LCMS m/z (M+H): 537.

Example 13.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-picolynoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

5



BB 0274010

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.01-2.08 (m, 3H), 2.12 (s, 3H), 3.08 (d, J=2.4 Hz, 2H), 3.17 (d, J=3.7 Hz, 2H), 3.63 (broadened singlet, 2H), 3.83-3.97 (m, 2H), 7.42 (d, J=7.8 Hz, 4H), 7.50 (t, J=5.8 Hz, 1H), 7.59 (d, J=7.7 Hz, 1H), 7.78 (d, J=13.8 Hz, 2H), 7.90-8.00 (m, 1H), 8.62 (d, J=4.3 Hz, 1H), 10.09 (broadened singlet, 1H),

Weight Yield - 0.072 g (29%)

LCMS m/z (M+H): 516.

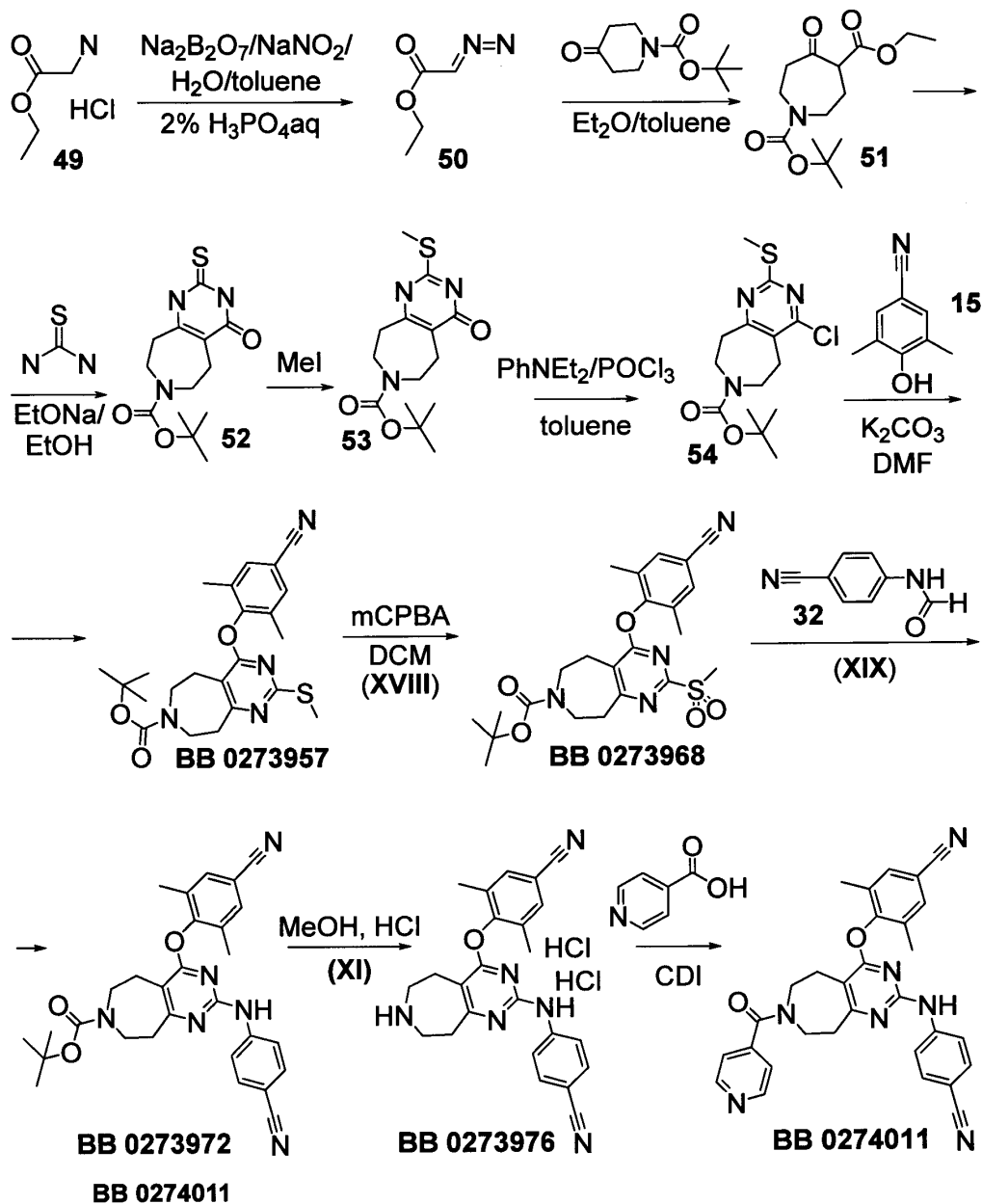
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Example 14.**Synthesis of 4-((2-((4-cyanophenyl)amino)-7-isonicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile**

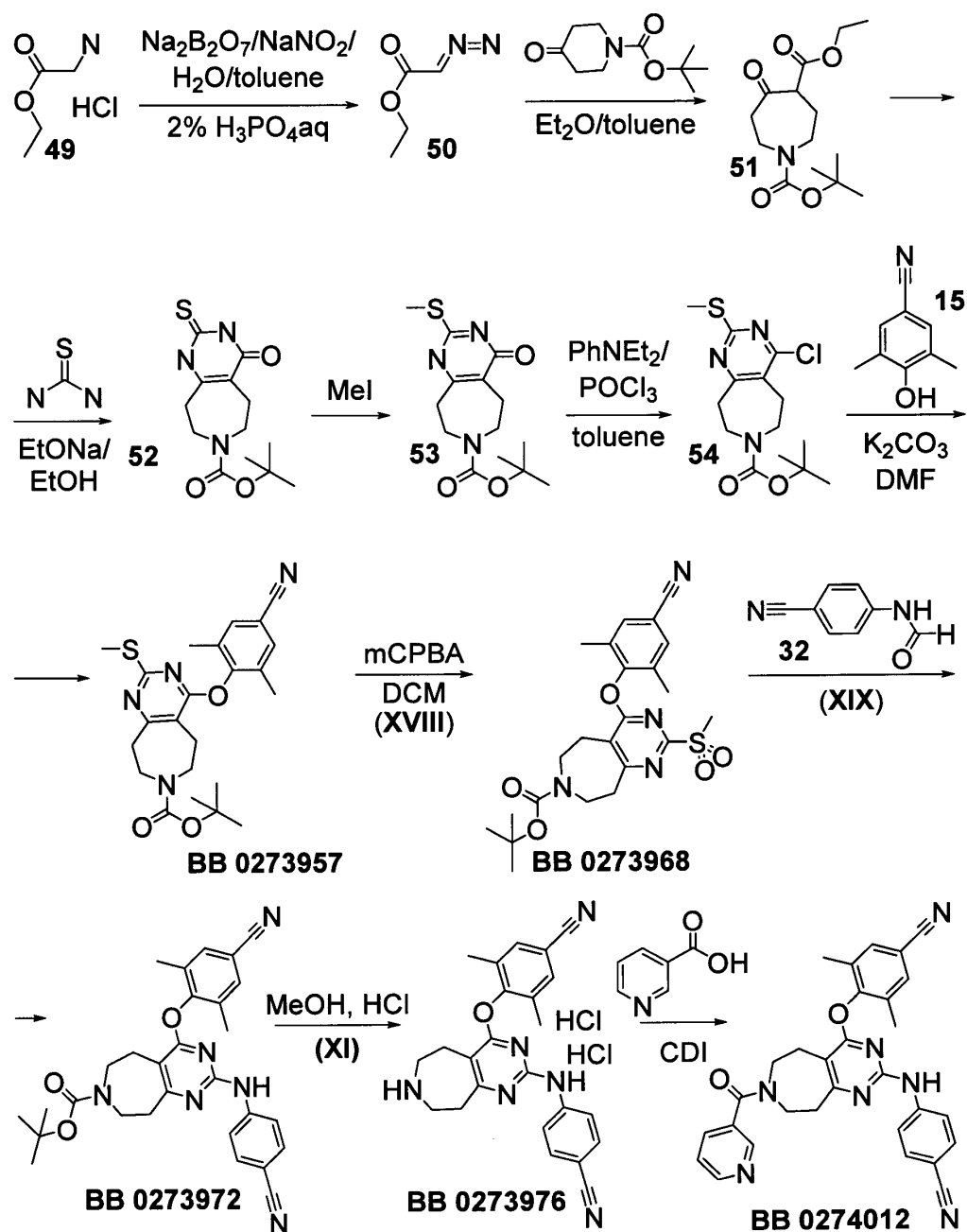
- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 2.05 (s, 3H), 2.12 (s, 3H), 3.05 (broadened singlet, 2H), 3.12-3.24 (m, 2H), 3.51 (broadened singlet, 2H), 3.82-3.96 (m, 2H), 7.32-7.51 (m, 6H), 7.78 (d, $J=14.6$ Hz, 2H), 8.69 (d, $J=4.8$ Hz, 2H), 10.10 (d, $J=4.0$ Hz, 1H).

Weight Yield - 0.067 g (32%)

LCMS m/z ($M+H$): 516.

Example 15.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-nicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0274012

$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$ δ , ppm): 2.04 (s, 3H), 2.12 (broadened singlet, 3H),

3.06 (broadened singlet, 2H), 3.19 (broadened singlet, 2H), 3.58 (broadened singlet, 2H), 3.90 (broadened singlet, 2H), 7.41 (d, $J=11.6$ Hz, 4H), 7.50 (dd, $J=7.5, 5.0$ Hz, 1H), 7.77 (d, $J=14.4$ Hz, 2H), 7.87 (d, $J=6.7$ Hz, 1H), 8.60-8.71 (m, 2H), 10.10 (broadened singlet, 1H).

5 Weight Yield - 0.055 g (30%)
 LCMS m/z (M+H): 516.

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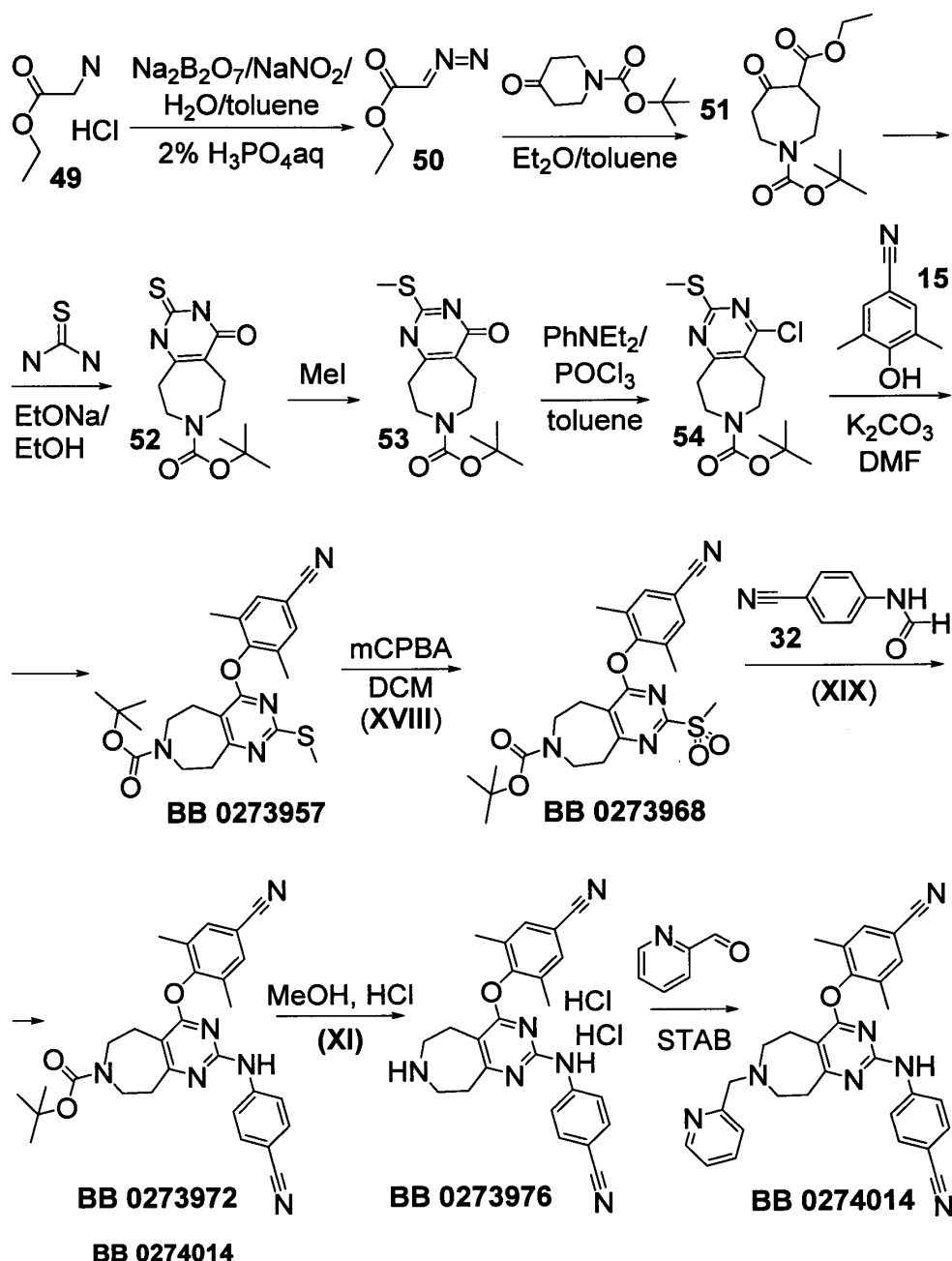
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Example 16.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(pyridine-2-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



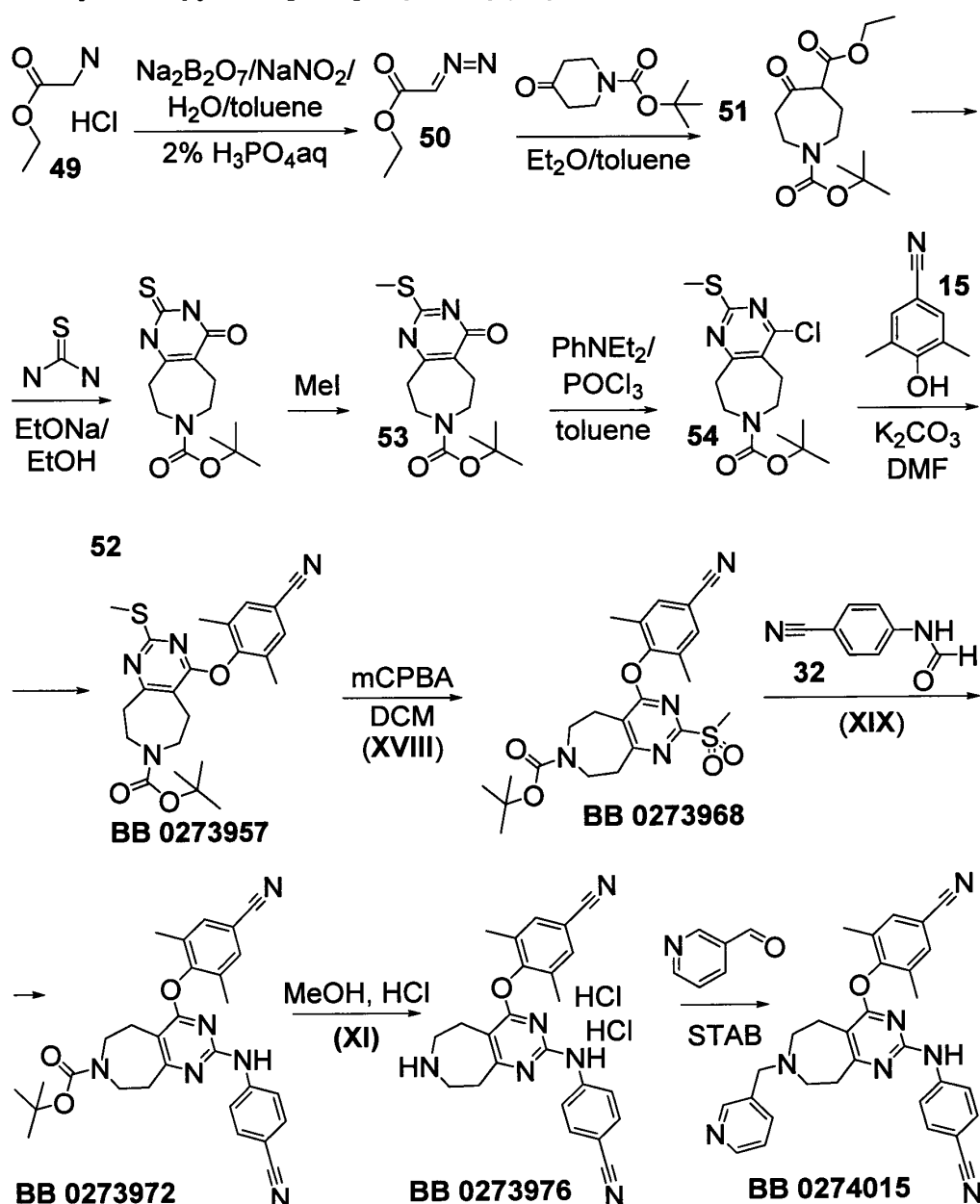
5 ^1H NMR (400 MHz, DMSO-d_6 , δ , ppm): 2.08 (s, 6H), 2.72 (d, $J=7.5$ Hz, 4H), 3.01 (d, $J=8.5$ Hz, 4H), 3.80 (s, 2H), 7.27 (dd, $J=6.7, 5.2$ Hz, 1H), 7.40 (s, 4H), 7.54 (d, $J=7.8$ Hz, 1H), 7.72-7.84 (m, 3H), 8.50 (d, $J=4.2$ Hz, 1H), 10.04 (s, 1H).

Weight Yield - 0.106 g (78%)

LCMS m/z (M+H): 502.

Example 17.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(pyridine-3-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274015

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.08 (s, 6H), 2.67 (d, *J*=6.3 Hz, 4H), 3.00 (dd, *J*=6.3, 2.6 Hz, 4H), 3.71 (s, 2H), 7.33-7.46 (m, 5H), 7.71-7.82 (m, 3H), 8.48 (dd, *J*=4.7, 1.5 Hz, 1H), 8.56 (d, *J*=1.5 Hz, 1H), 10.04 (s, 1H).

5 Weight Yield - 0.090 g (64%)

LCMS *m/z* (M+H): 502

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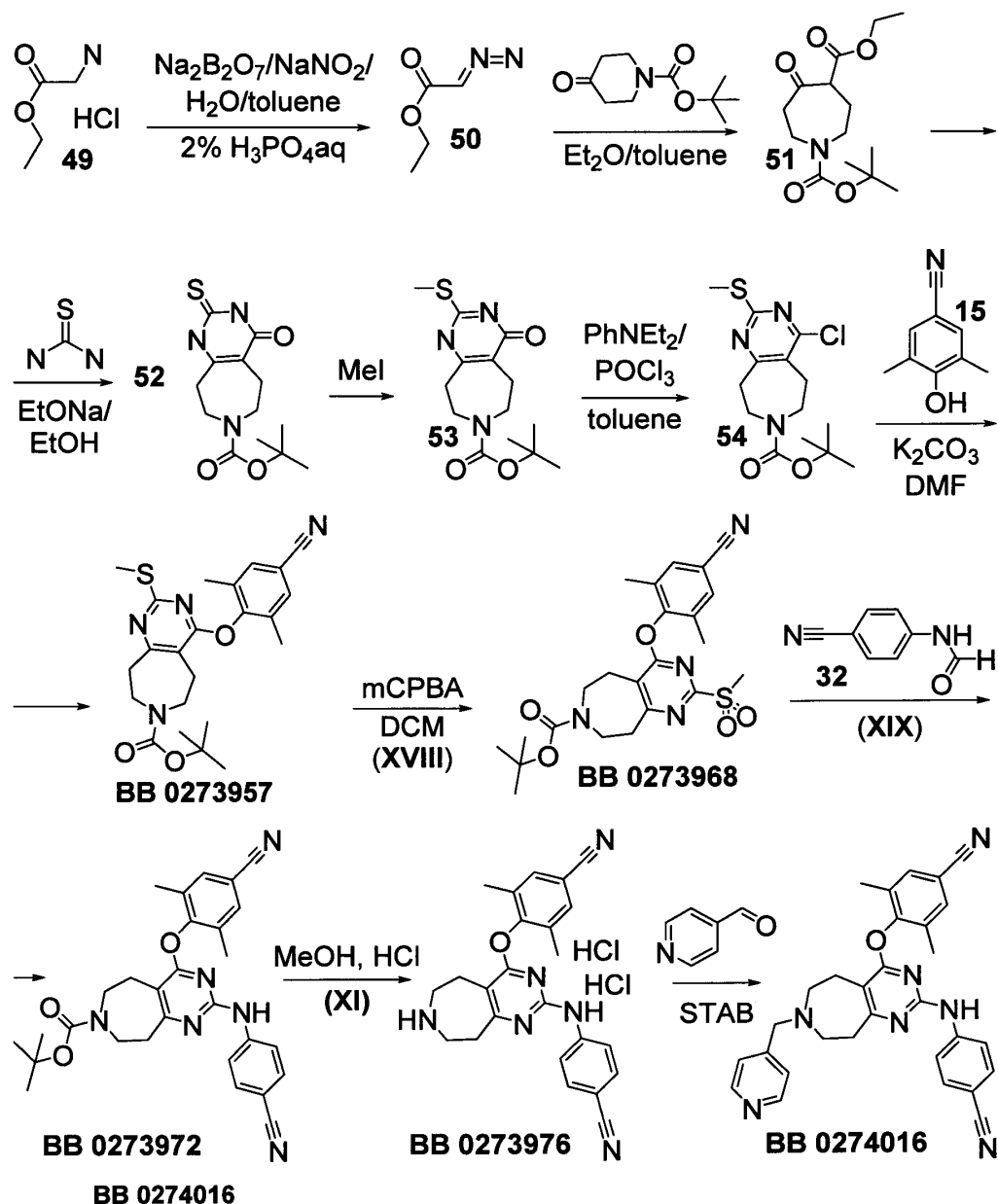
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Example 18.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(pyridine-4-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

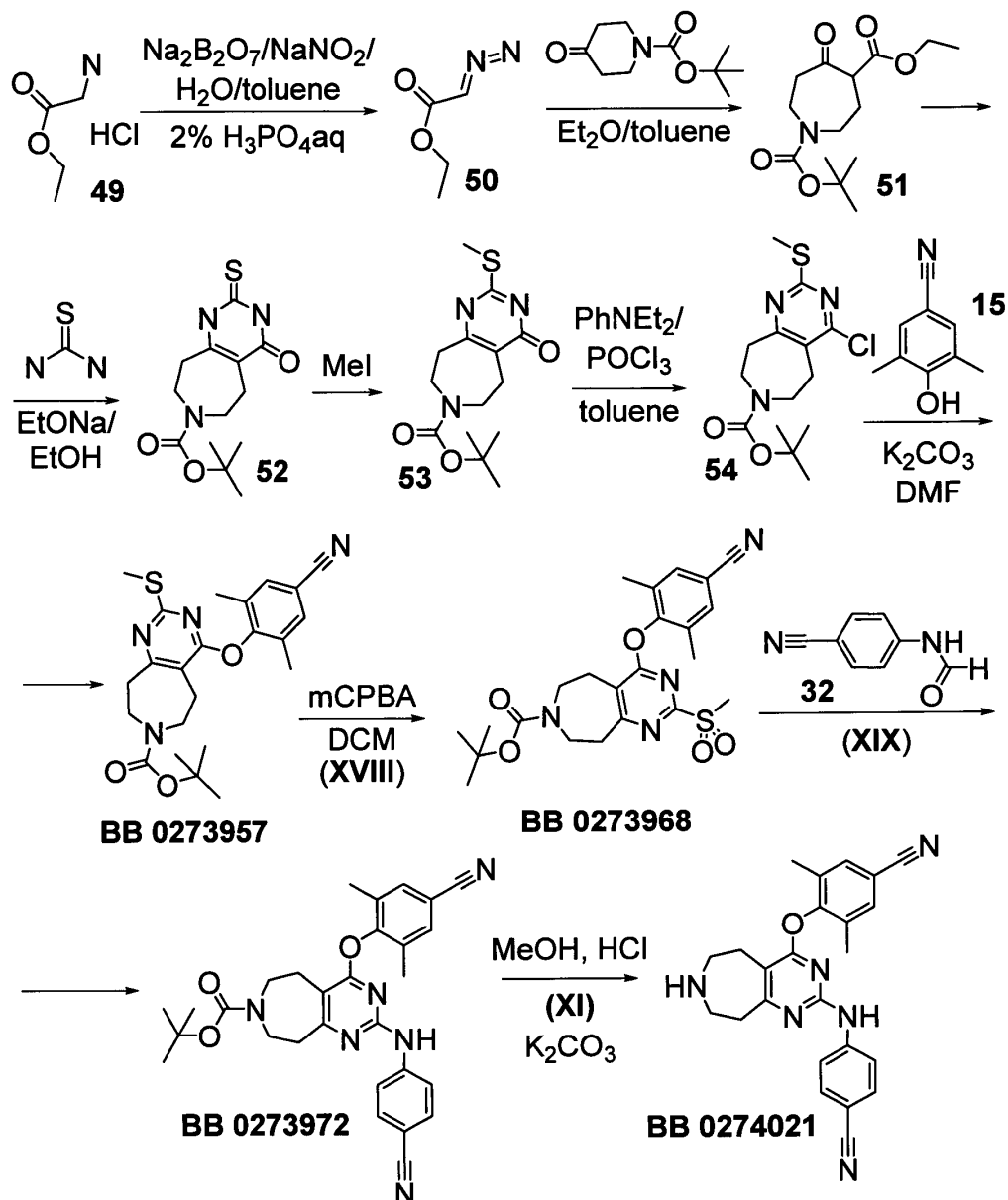


5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 2.09 (s, 6H), 2.68 (d, $J=5.8$ Hz, 4H), 3.02 (d, $J=6.2$ Hz, 4H), 3.72 (s, 2H), 7.33-7.46 (m, 6H), 7.78 (s, 2H), 8.54 (d, $J=5.6$, 2H), 10.04 (s, 1H).

Weight Yield - 0.095 g (66%)

LCMS m/z ($M+H$): 502.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0274021

^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.09 (broadened singlet, 6H), 2.73-3.08 (m, 8H), 7.41 (broadened singlet, 4H), 7.77 (broadened singlet, 2H), 9.99 (broadened singlet, 1H),

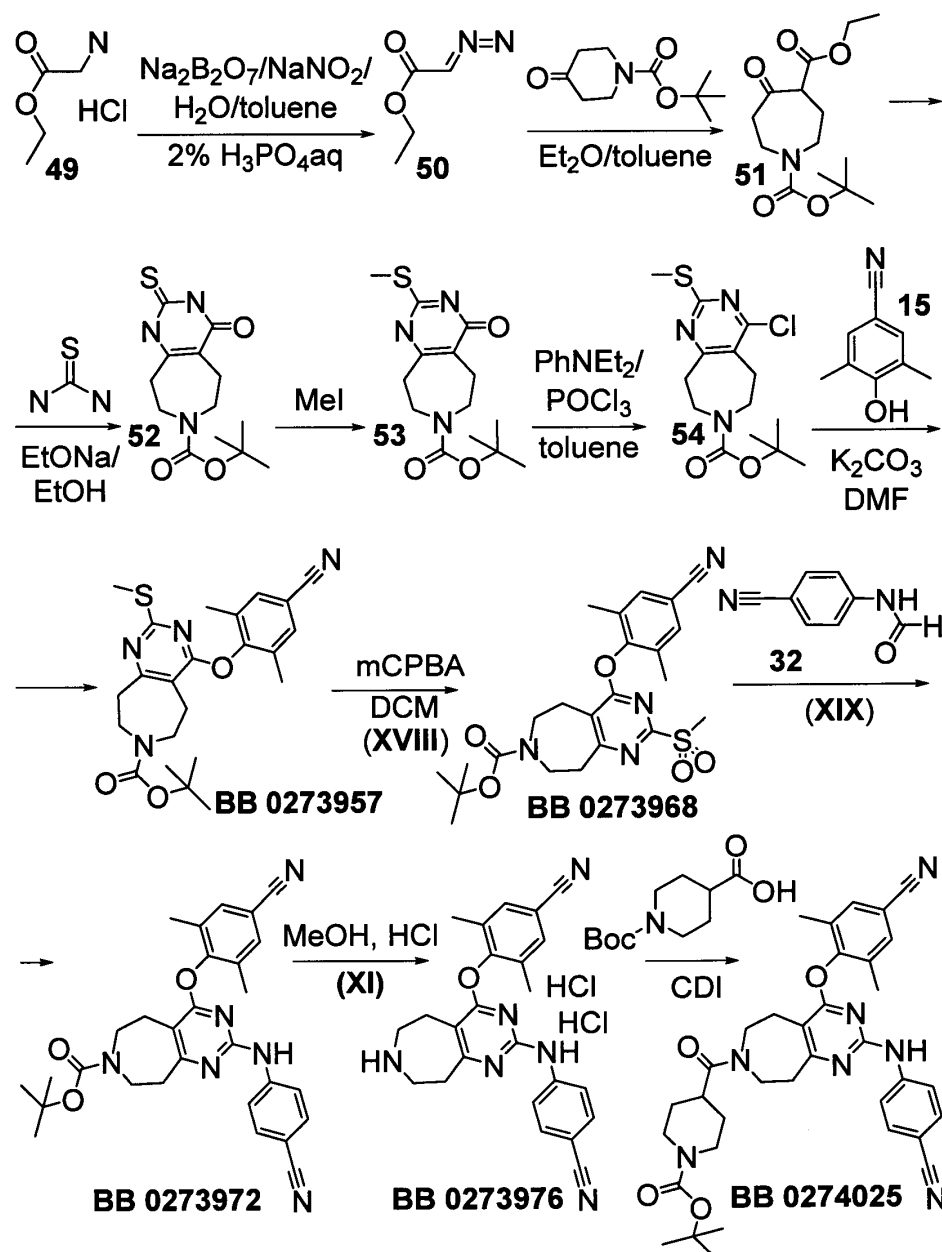
Weight Yield - 0.174 g (96%)

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LCMS m/z (M+H): 411

Example 19.

Synthesis of *tert*-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]asein-7-carbonyl)piperidine-1-carboxylate



5

BB 0274025

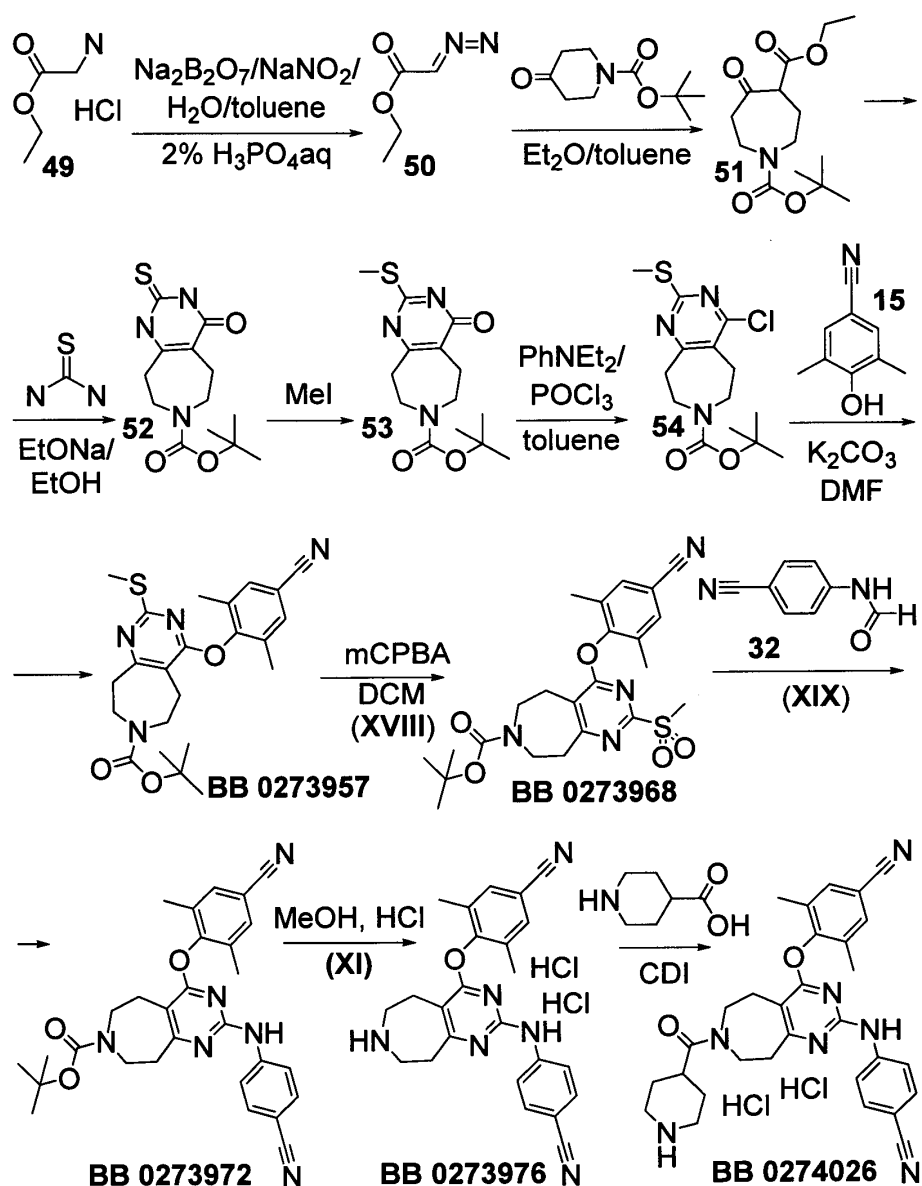
^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.47 (s, 9H), 1.64-1.90 (m, 5H), 2.14 (d, $J=1.6$ Hz, 6H), 2.64-2.89 (m, 3H), 3.03-3.22 (m, 4H), 3.70-3.91 (m, 4H), 4.05-4.34 (m, 2H), 7.05-

7.16 (m, 1H), 7.33 (t, $J=8.4$ Hz, 2H), 7.36-7.42 (m, 2H), 7.48 (d, $J=4.5$ Hz, 2H).

Weight Yield - 0.230 g (55%)

LCMS m/z (M+H): 622.

5 **Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(piperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile dihydrochloride**



BB 0274026

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.78 (broadened singlet, 4H), 2.09 (broadened singlet, 6H), 2.81-3.16 (m, 7H), 3.23 (broadened singlet, 2H), 3.62-3.90 (m, 4H), 7.41 (broadened singlet, 4H), 7.78 (broadened singlet, 2H), 8.86 (broadened singlet, 1H), 9.27 (broadened singlet, 1H), 10.08 (broadened singlet, 1H).

Weight Yield - 0.090 g (80%)

LCMS m/z (M+H): 522.

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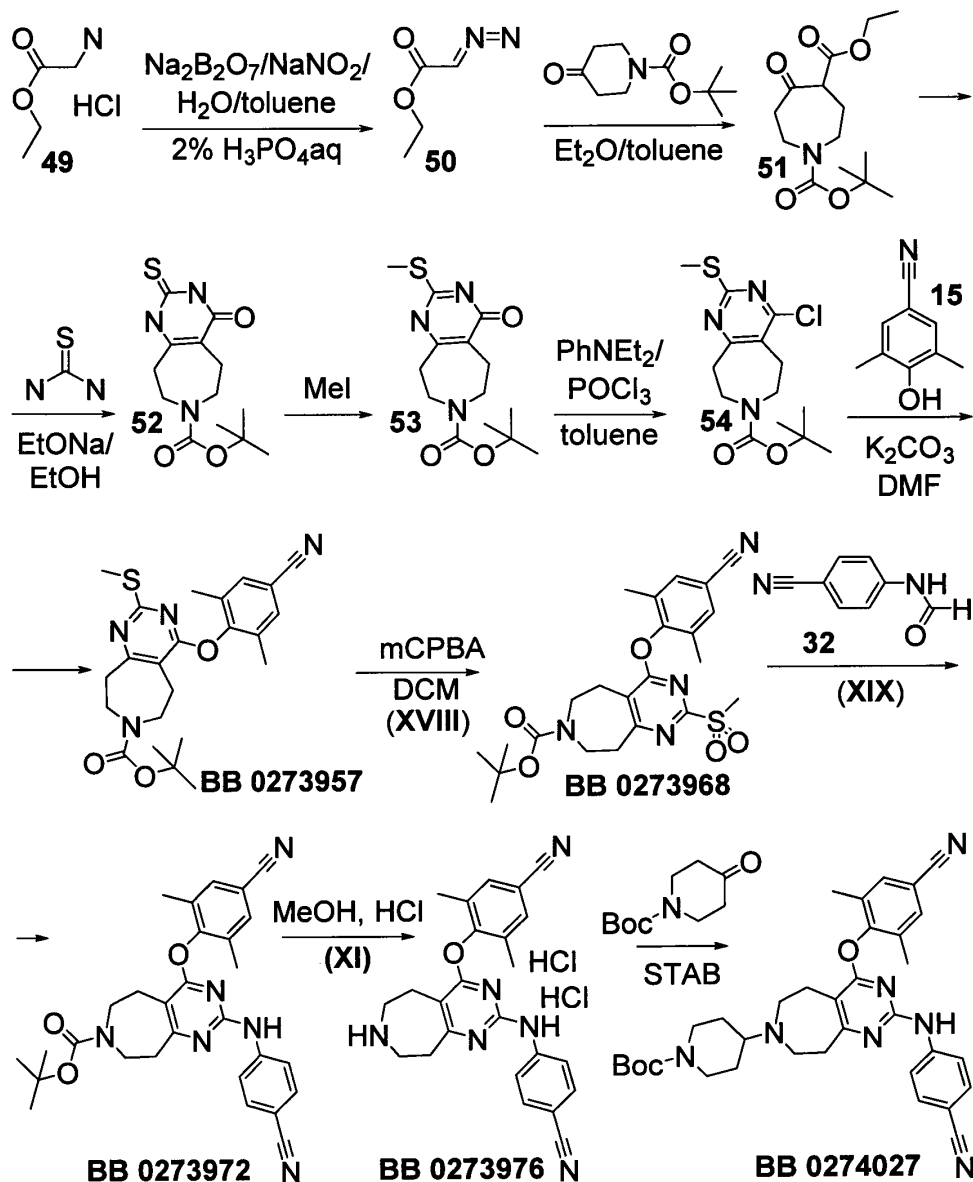
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Example 20.

Synthesis of *tert*-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)piperidine-1-carboxylate



5

BB 0274027

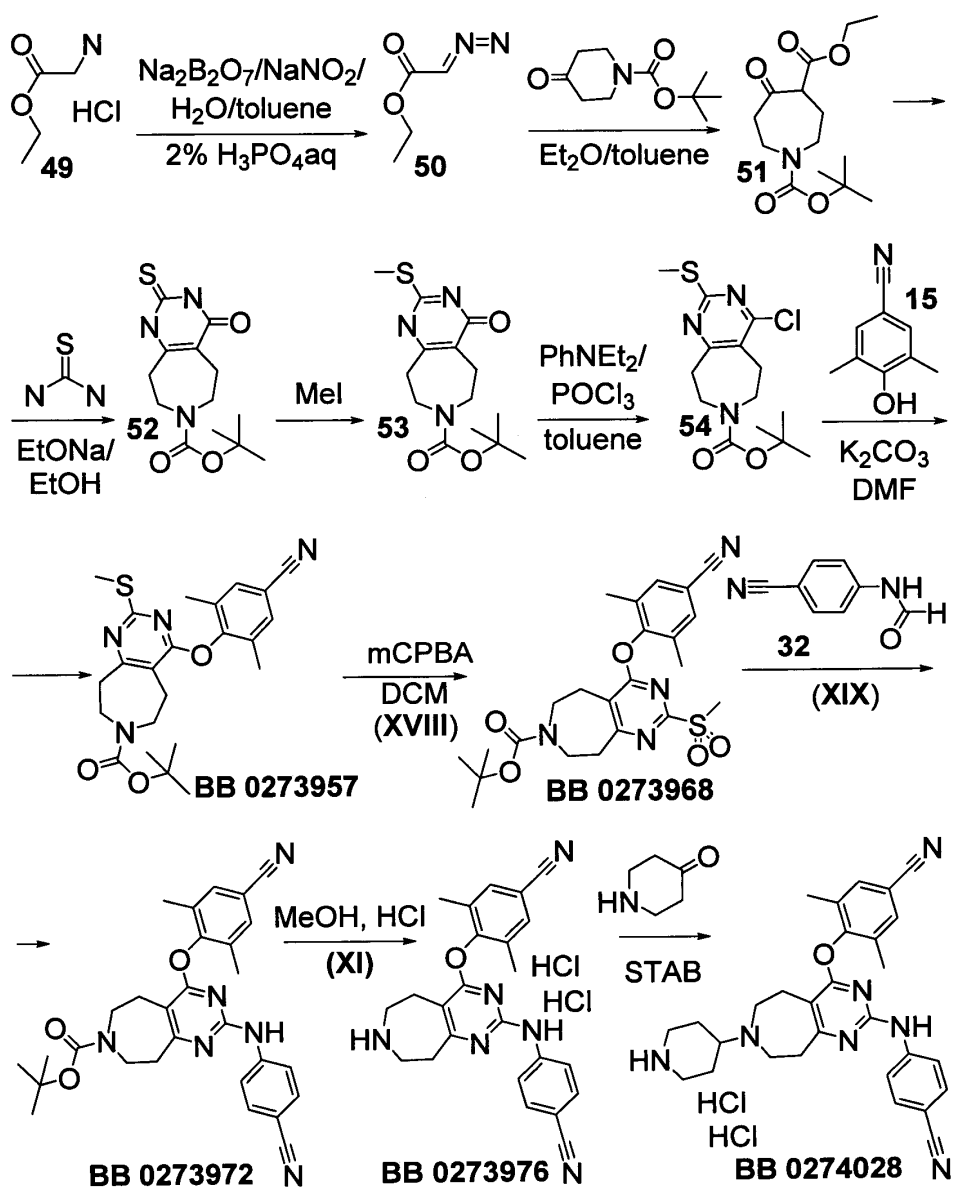
^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 1.26-1.46 (m, 11H), 1.68 (d, $J=11.0$ Hz, 2H), 2.08 (s, 6H), 2.58-2.83 (m, 7H), 2.94 (broadened singlet, 4H), 3.91-4.08 (m, 2H), 7.41 (s, 4H), 7.78 (s, 2H), 10.01 (s, 1H).

Weight Yield - 0.203 g (82%)

LCMS m/z (M+H): 594.

Example 21.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(piperidine-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile trihydrochloride



BB 0274028

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.97-2.19 (m, 8H), 2.35 (d, J=11.9 Hz, 2H), 2.94 (kv, J=11.1 Hz, 2H), 3.09 (dd, J=16.5, 6.54 Hz, 1H), 3.24-3.36 (m, 1H), 3.37-3.53 (m, 5H), 3.58-3.70 (m, 2H), 3.71-3.87 (m, 2H), 7.44 (s, 4H), 7.79 (s, 2H), 9.25 (d, J=10.2 Hz, 1H), 9.40 (d, J=9.1 Hz, 1H), 10.14 (broadened singlet, 1H), 12.13 (broadened singlet, 1H).

Weight Yield - 0.182 g (87%)

LCMS m/z (M+H): 494.

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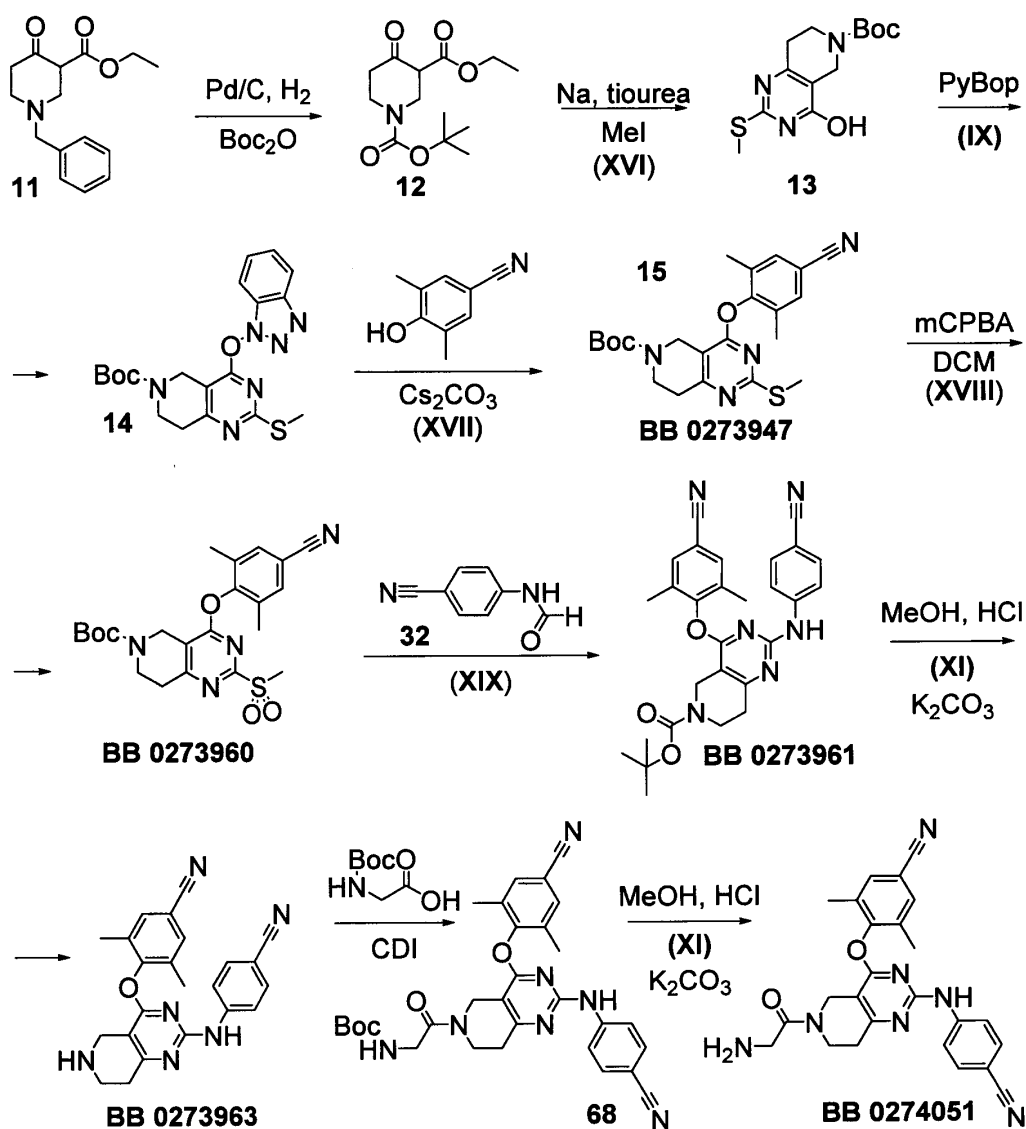
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Example 22.

Synthesis of 4-((6-(2-aminoacetyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0274051

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.18 (s, 6H), 2.82 - 3.11 (m, 2H), 3.56 - 3.88 (m, 2H), 3.90 - 4.27 (m, 2H), 4.49 - 4.87 (m, 2H), 7.41 (s, 4H), 7.49 (s, 2H).

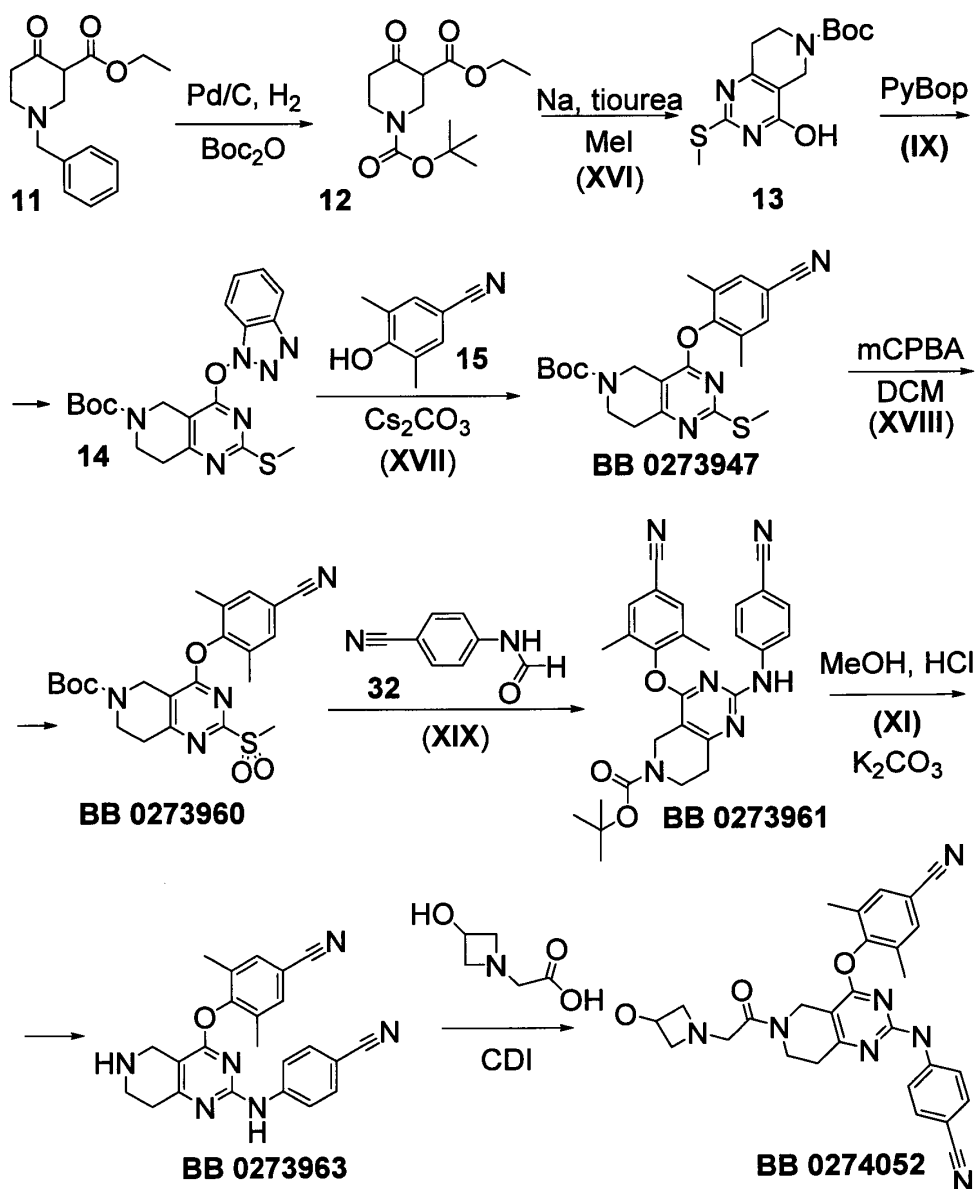
Weight Yield - 0.029 g (26%)

10

LCMS m/z ($\text{M}+\text{H}$): 453

Example 23.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(2-(3-hydroxyazetidine-1-yl)acetyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0274052

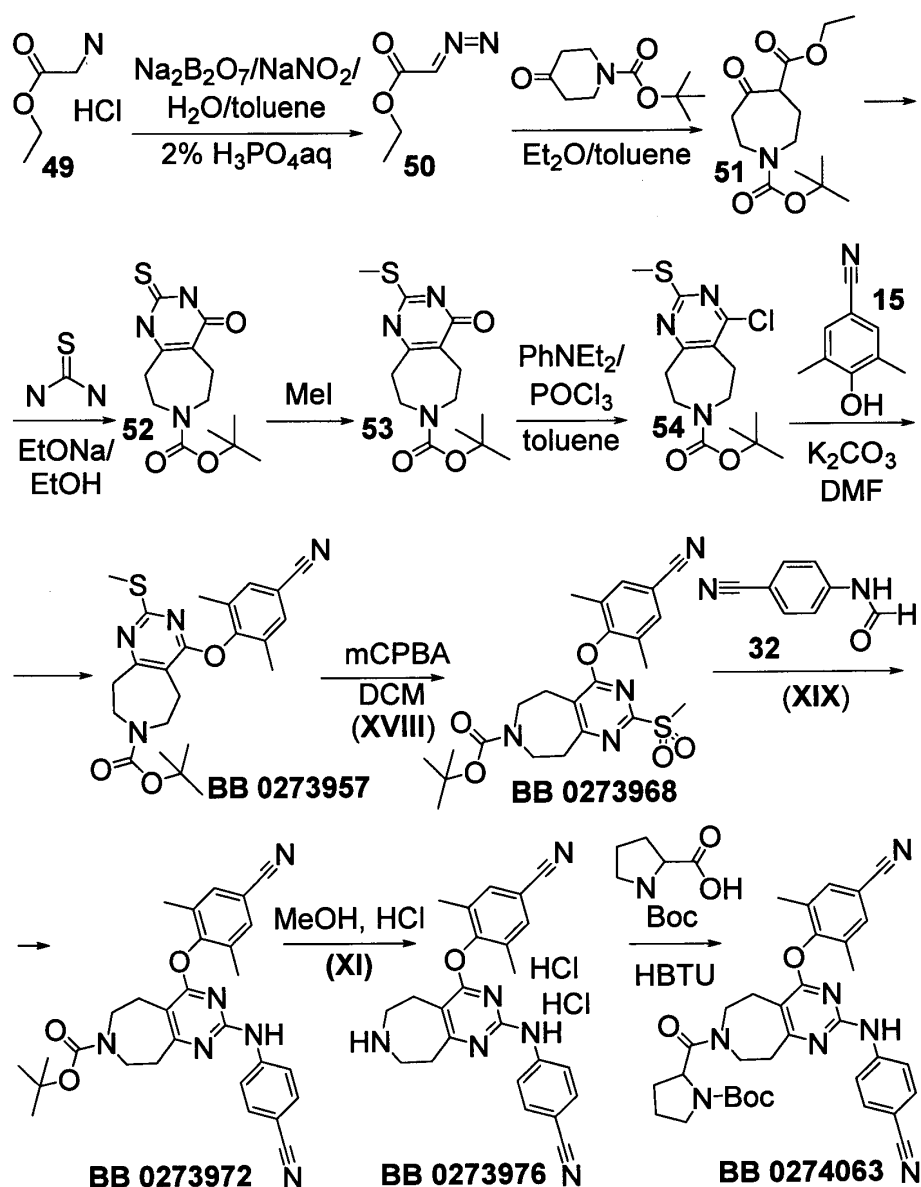
¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.90 (broadened singlet, 1H), 2.34 (broadened singlet, 1H), 2.57 - 2.69 (m, 2H), 3.12 - 3.28 (m, 2H), 3.43 - 3.55 (m, 2H), 3.57 - 3.74 (m, 2H), 3.94 - 4.24 (m, 1H), 4.31 - 4.54 (m, 2H), 4.65 - 4.88 (m, 1H), 7.05 (d, J=7.5 Hz, 2H), 7.19 (d, J=7.1 Hz, 2H), 7.26 (s, 2H).

Weight Yield - 0.005 g (12%)

LCMS m/z (M+H): 510

Example 24.

Synthesis of *tert*-butyl-2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate



BB 0274063

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.25 (broadened singlet, 9H), 1.36 (s, 3H), 1.59-1.91 (m, 3H), 2.02-2.14 (m, 6H), 2.14-2.33 (m, 1H), 2.74-3.33 (m, 5H), 3.36-4.06 (m, 5H), 4.58-4.78 (m, 1H), 7.41 (broadened singlet, 4H), 7.78 (broadened singlet, 2H), 9.96-10.16 (m, 1H).

Weight Yield - 0.128 g (57%)

LCMS m/z (M+H): 608

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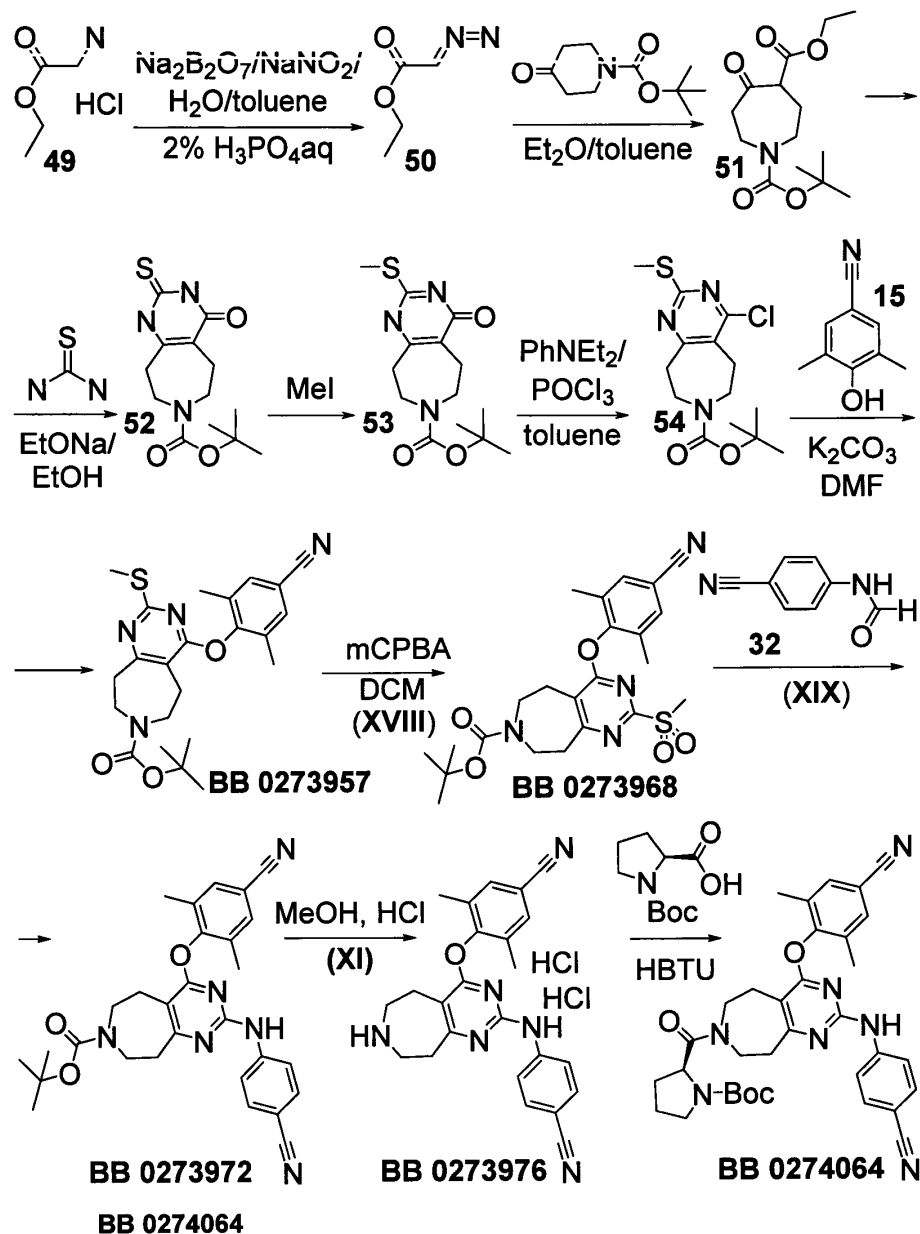
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Example 25.

Synthesis of (R)-tert-butyl-2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate



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BB 0274064

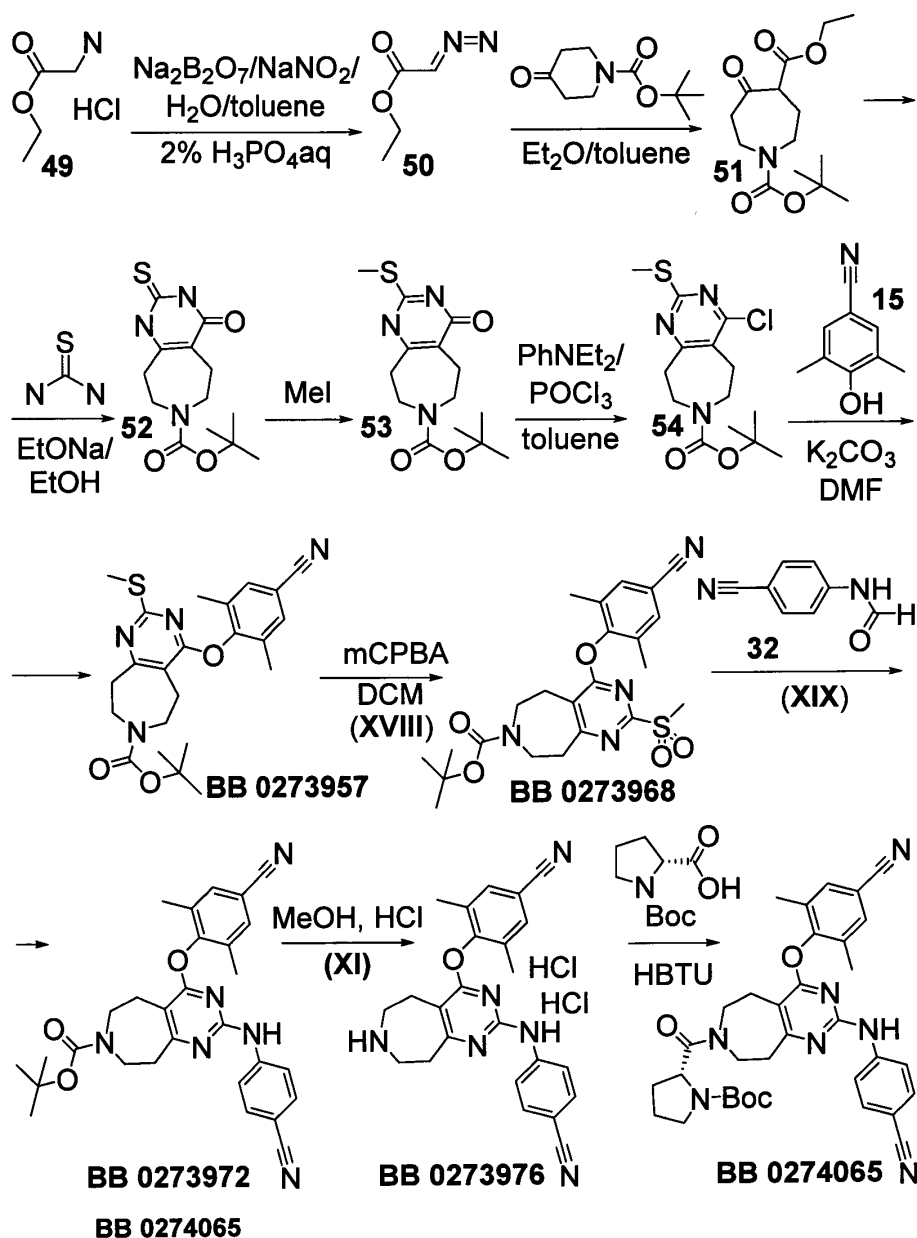
^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 1.25 (broadened singlet, 6H), 1.36 (s, 3H), 1.58-1.91 (m, 3H), 2.02-2.15 (m, 6H), 2.15-2.34 (m, 1H), 2.76-3.32 (m, 5H), 3.36-4.05 (m, 5H), 4.54-4.79 (m, 1H), 7.41 (broadened singlet, 4H), 7.78 (d, $J=2.4$ Hz, 2H), 9.97-10.17 (m, 1H).

Weight Yield - 0.103 g (52%)

LCMS m/z (M+H): 608.

Example 26.

Synthesis of (S)-tert-butyl-2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate



105

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.25 (broadened singlet, 6H), 1.36 (s, 3H), 1.58-1.92 (m, 3H), 2.03-2.14 (m, 6H), 2.14-2.34 (m, 1H), 2.79-3.33 (m, 5H), 3.35-4.03 (m, 5H), 4.53-4.78 (m, 1H), 7.41 (broadened singlet, 4H), 7.77 (broadened singlet, 2H), 9.93-10.16 (m, 1H).

5 Weight Yield - 0.098 g (50%)

LCMS m/z (M+H): 608

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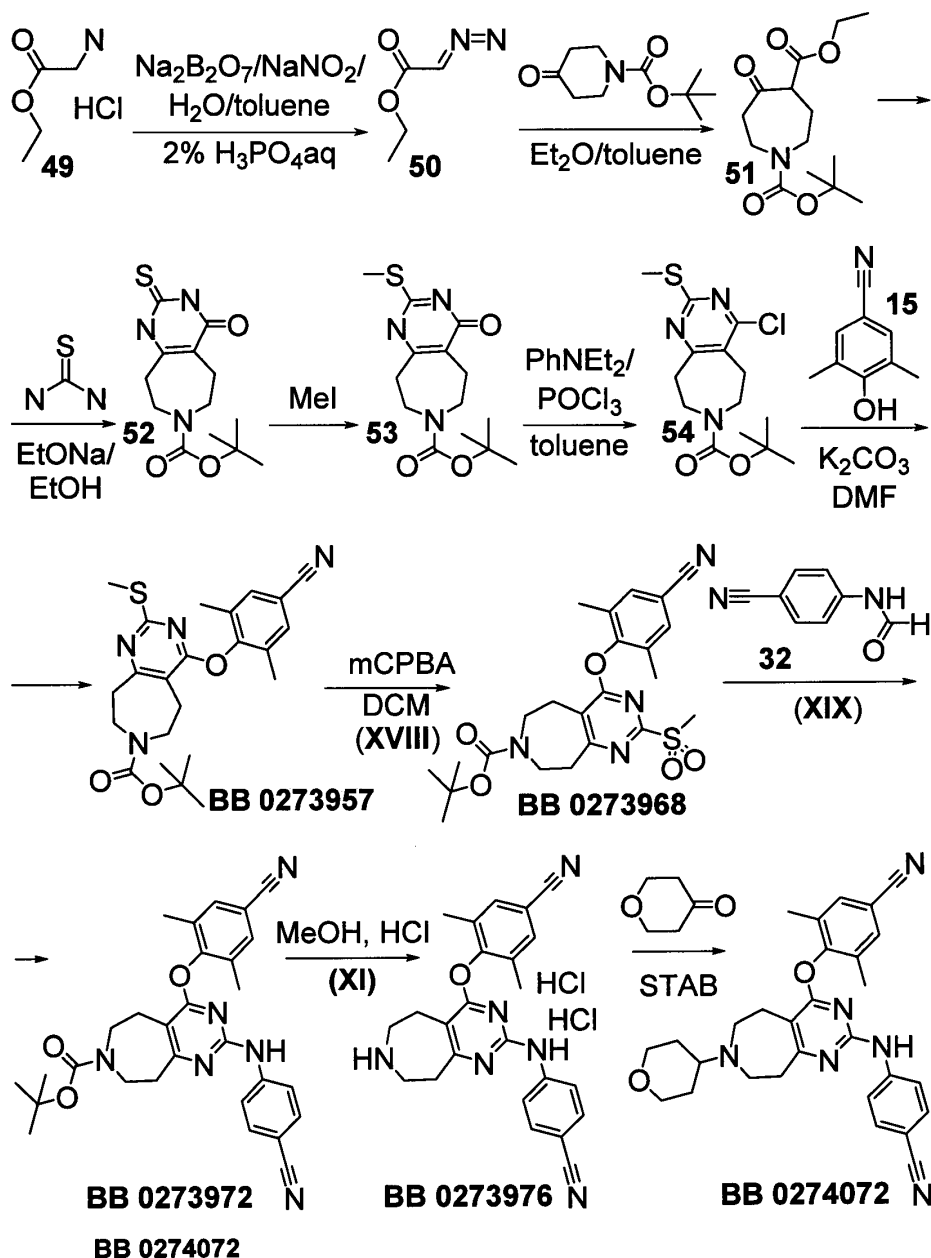
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Example 27.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



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BB 0274072

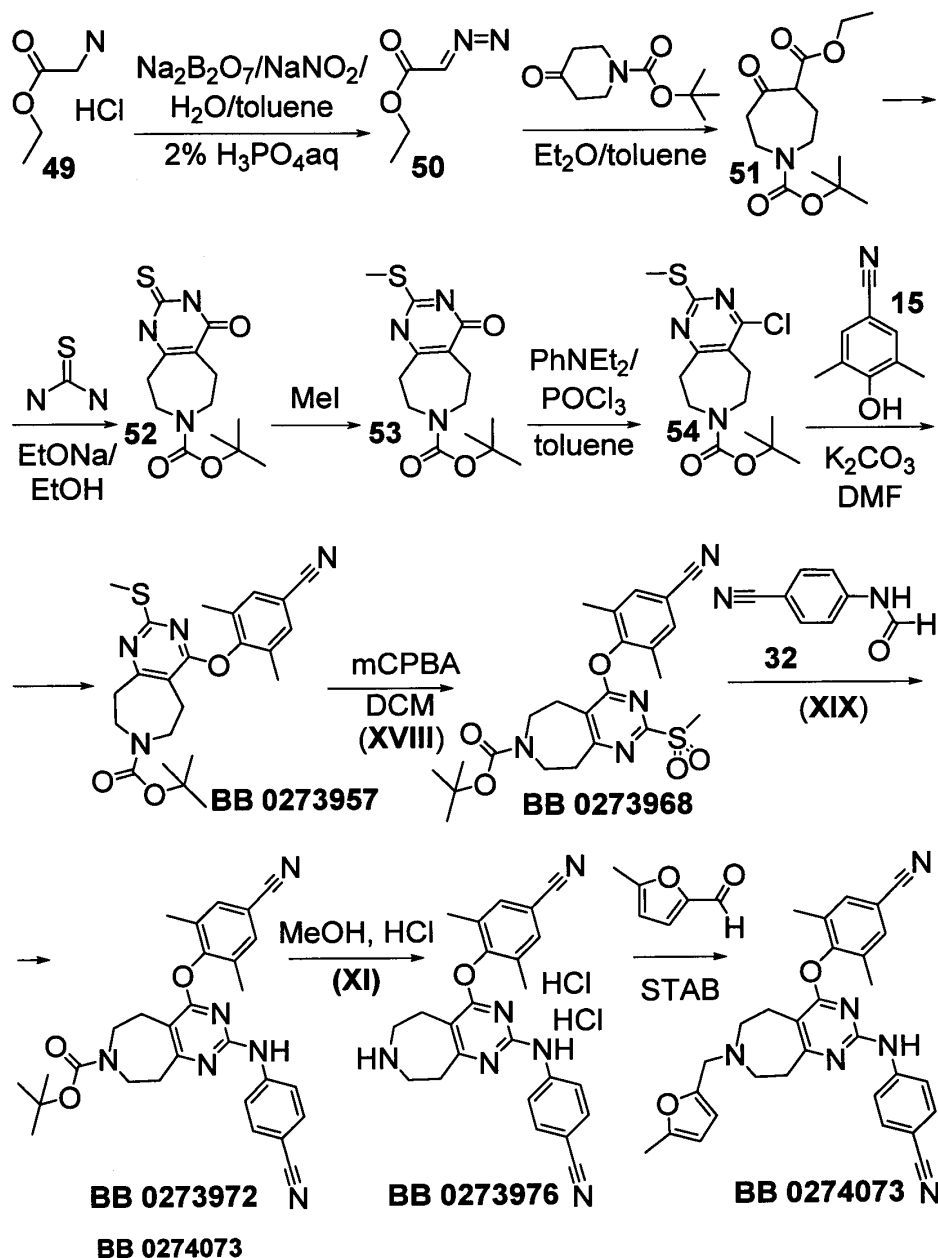
^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 1.40-1.74 (m, 4H), 2.09 (s, 6H), 2.77 (broadened singlet, 4H), 2.97 (broadened singlet, 4H), 3.19-3.46 (m, 3H), 3.81-3.96 (m, 2H), 7.41 (s, 4H), 7.78 (s, 2H), 10.00 (broadened singlet, 1H).

Weight Yield - 0.096 g (82%)

LCMS m/z (M+H): 495

Example 28.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(5-methylfuran-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



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BB 0274073

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.14 (s, 6H), 2.30 (s, 3H), 2.64-2.82 (m, 4H), 3.08 (d, $J=6.7$ Hz, 4H), 3.68 (s, 2H), 5.92 (broadened singlet, 1H), 6.11 (d, $J=2.8$ Hz, 1H),

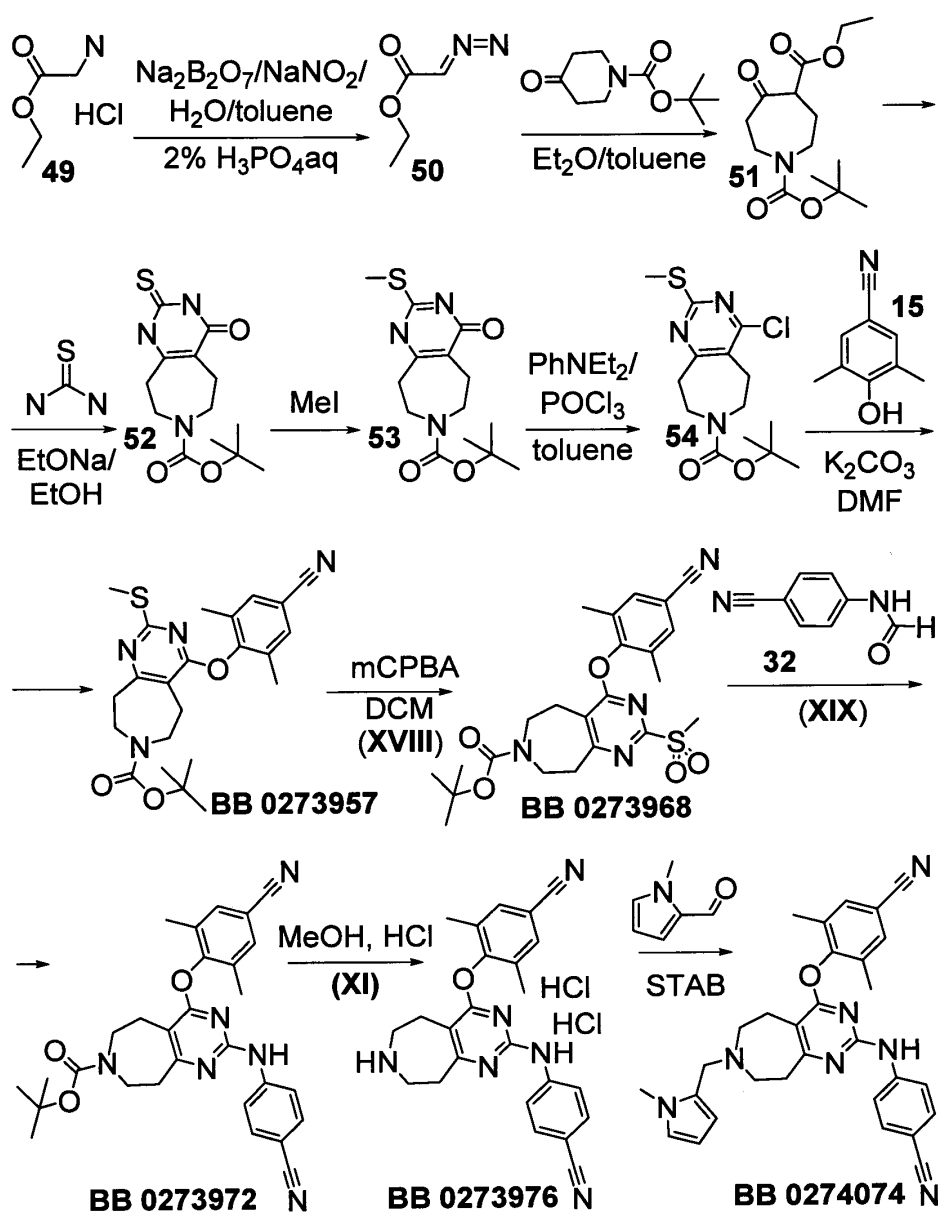
7.14 (s, 1H), 7.24-7.33 (m, 2H), 7.34-7.41 (m, 2H), 7.47 (m, 2H).

Weight Yield - 0.038 g (44%)

LCMS m/z (M+H): 505

Example 29.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(1-methyl-1H-pyrrol-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274074

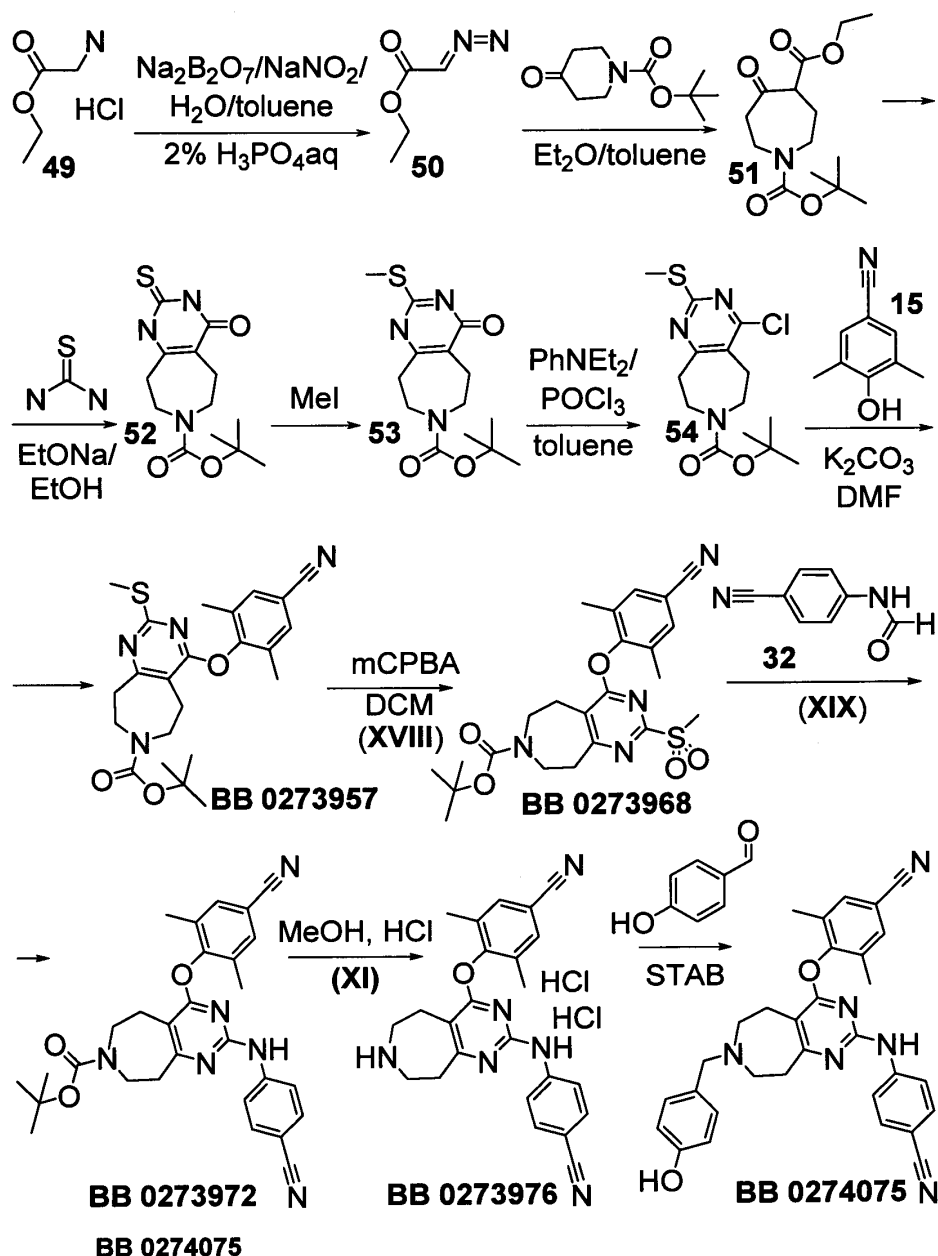
¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.15 (s, 6H), 2.68 (dd, *J*=12.2 Hz, 10.3 Hz, 4H), 2.94-3.14 (m, 4H), 3.59 (s, 2H), 3.74 (s, 3H), 6.00-6.05 (m, 1H), 6.07 (t, *J*=3.0 Hz, 1H), 6.61-6.70 (m, 1H), 7.12 (s, 1H), 7.24-7.33 (m, 2H), 7.34-7.42 (m, 2H), 7.48 (s, 2H).

Weight Yield - 0.152 g (38%)

LCMS *m/z* (M+H): 504

Example 30.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(4-hydroxybenzyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



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BB 0274075

^1H NMR (400 MHz, DMSO-d_6 , δ , ppm): 2.08 (s, 6H), 2.62 (broadened singlet, 4H), 2.98 (broadened singlet, 4H), 3.53 (broadened singlet, 2H), 6.72 (d, $J=8.3$ Hz, 2H), 7.14 (d, $J=8.0$ Hz, 2H), 7.40 (s, 4H), 7.77 (s, 2H), 9.30 (broadened singlet, 1H), 10.03 (s, 1H).

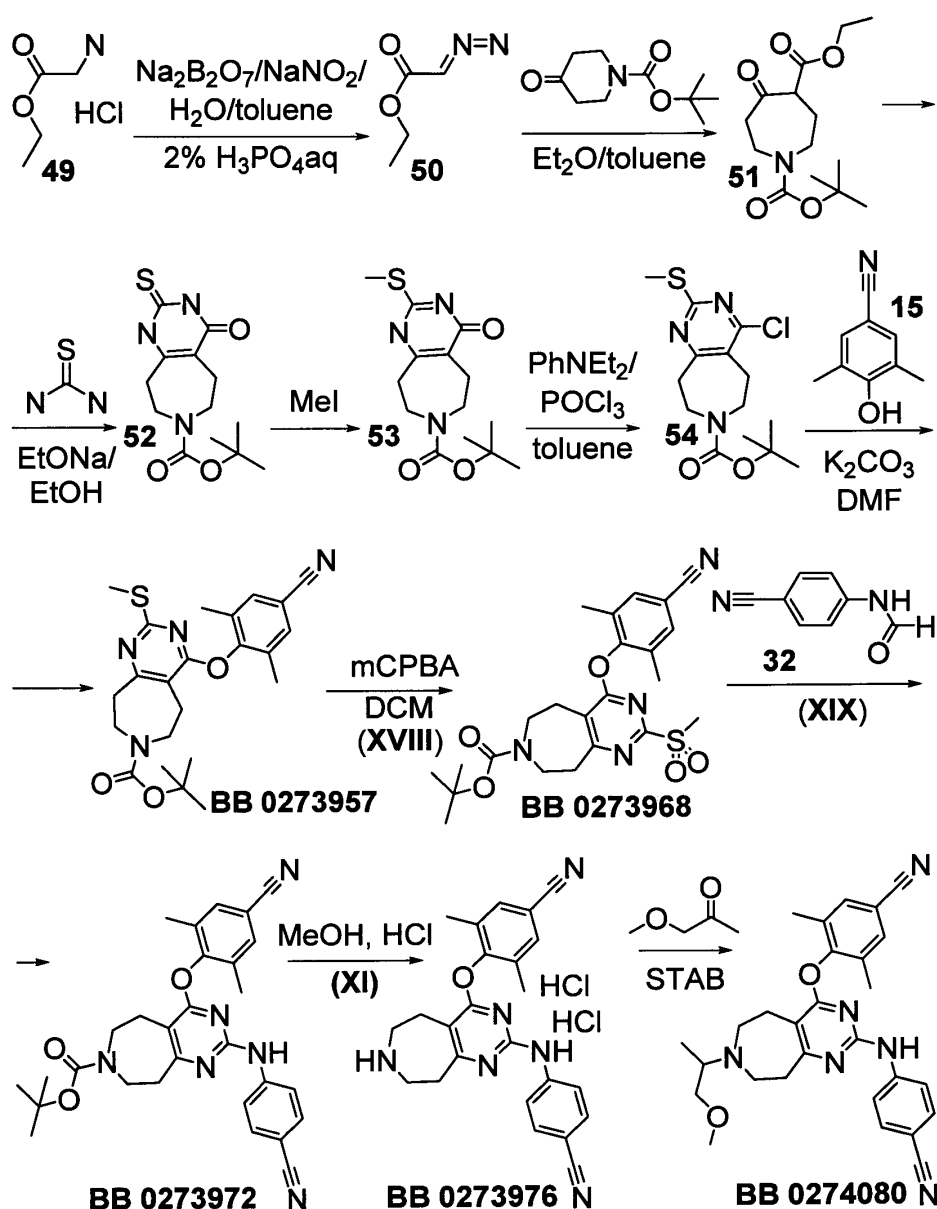
Weight Yield - 0.042 g (24%)

LCMS m/z (M+H): 517

Example 31.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(1-methoxypropane-2-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

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BB 0274080

¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.06 (d, *J*=5.8 Hz, 3H), 2.04-2.27 (m, 6H),
2.81 (broadened singlet, 4H), 3.04 (broadened singlet, 5H), 3.32 (broadened singlet, 1H),
5 3.36 (broadened singlet, 3H), 3.51 (d, *J*=6.7 Hz, 1H), 7.14 (broadened singlet, 1H), 7.24-
7.33 (m, 2H), 7.36 (d, *J*=7.90 Hz, 2H), 7.47 (broadened singlet, 2H).

Weight Yield - 0.128 g (48%)

LCMS *m/z* (M+H): 483

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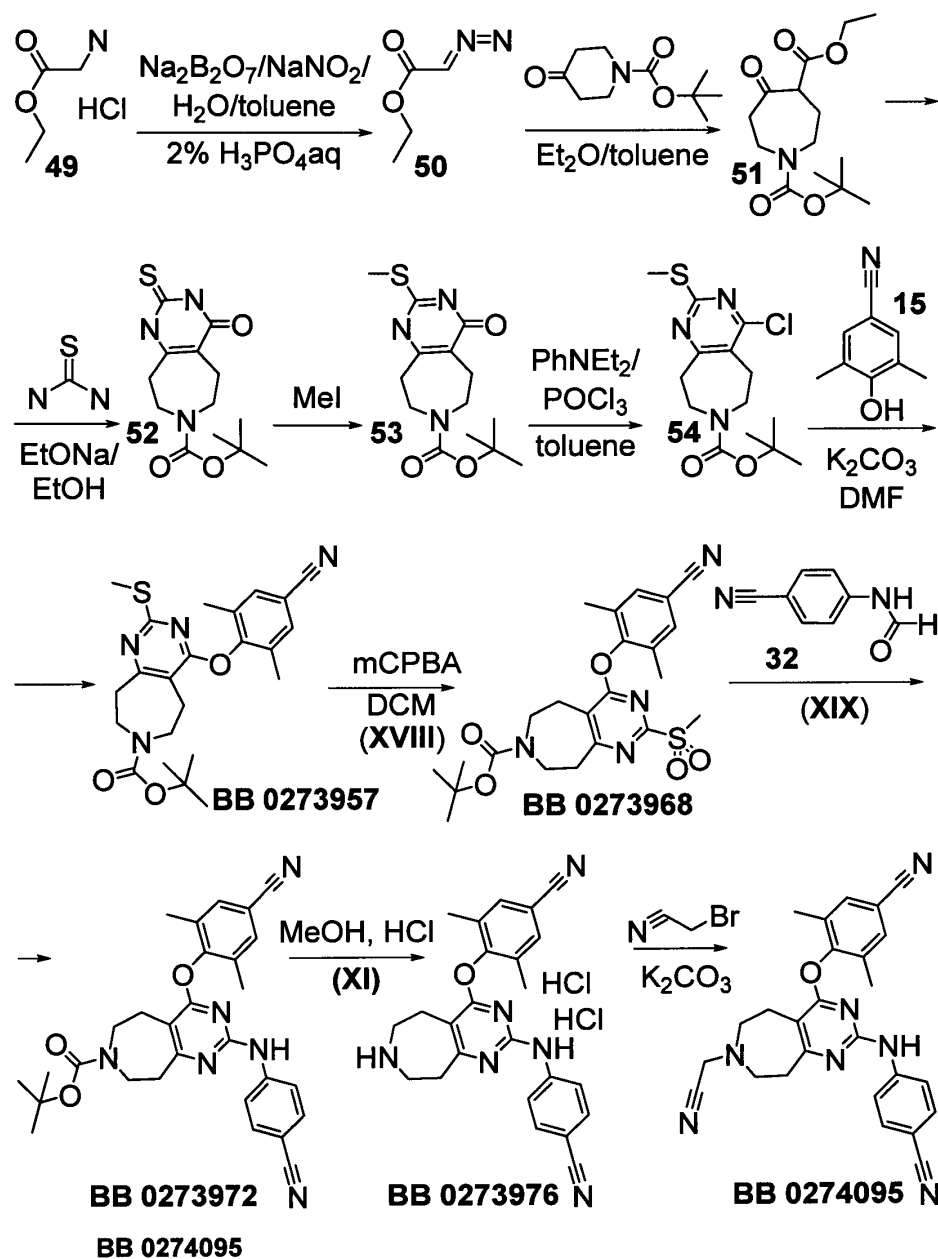
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Example 32.

Synthesis of 4-((7-(cyanomethyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274095

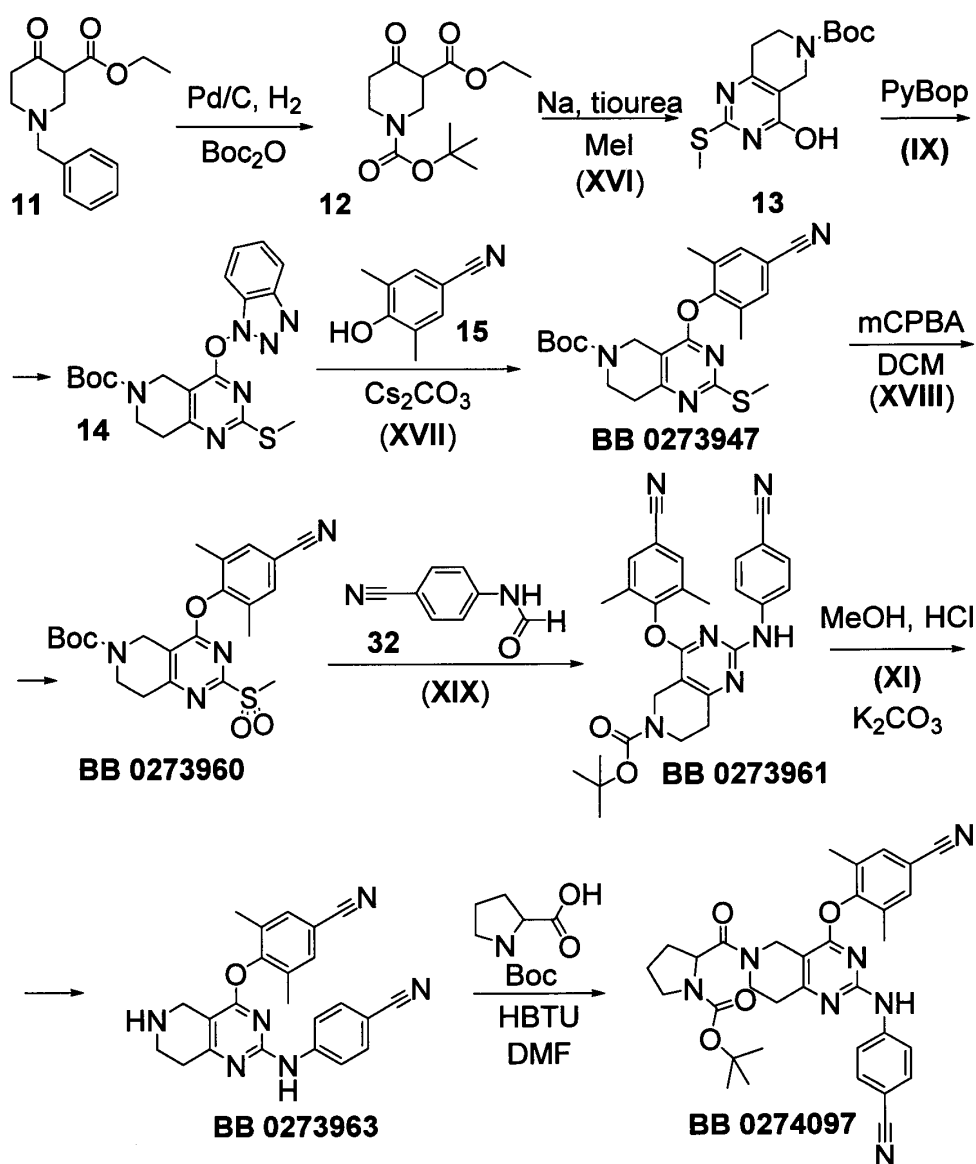
^1H NMR (400 MHz, DMSO-d_6 , δ , ppm): 2.10 (s, 6H), 2.72 (broadened singlet, 4H), 3.03 (broadened singlet, 4H), 3.89 (s, 2H), 7.42 (broadened singlet, 4H), 7.78 (s, 2H), 10.05 (broadened singlet, 1H).

Weight Yield - 0.042 g (24%)

LCMS m/z (M+H): 450

Example 33.

Synthesis of *tert*-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-6-carbonyl)pyrrolidine-1-carboxylate

**BB 0274097**

¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.40 - 1.48 (m, 9H), 2.18 (s, 6H), 2.80 - 3.09 (m, 2H), 3.64 - 4.00 (m, 2H), 4.59 - 4.92 (m, 2H), 5.25 - 5.63 (m, 1H), 7.34 - 7.44 (m, 4H),

115

7.48 (s, 2 H).

Weight Yield - 0.068 g (67%)

LCMS m/z (M+H): 494 (M-Boc).

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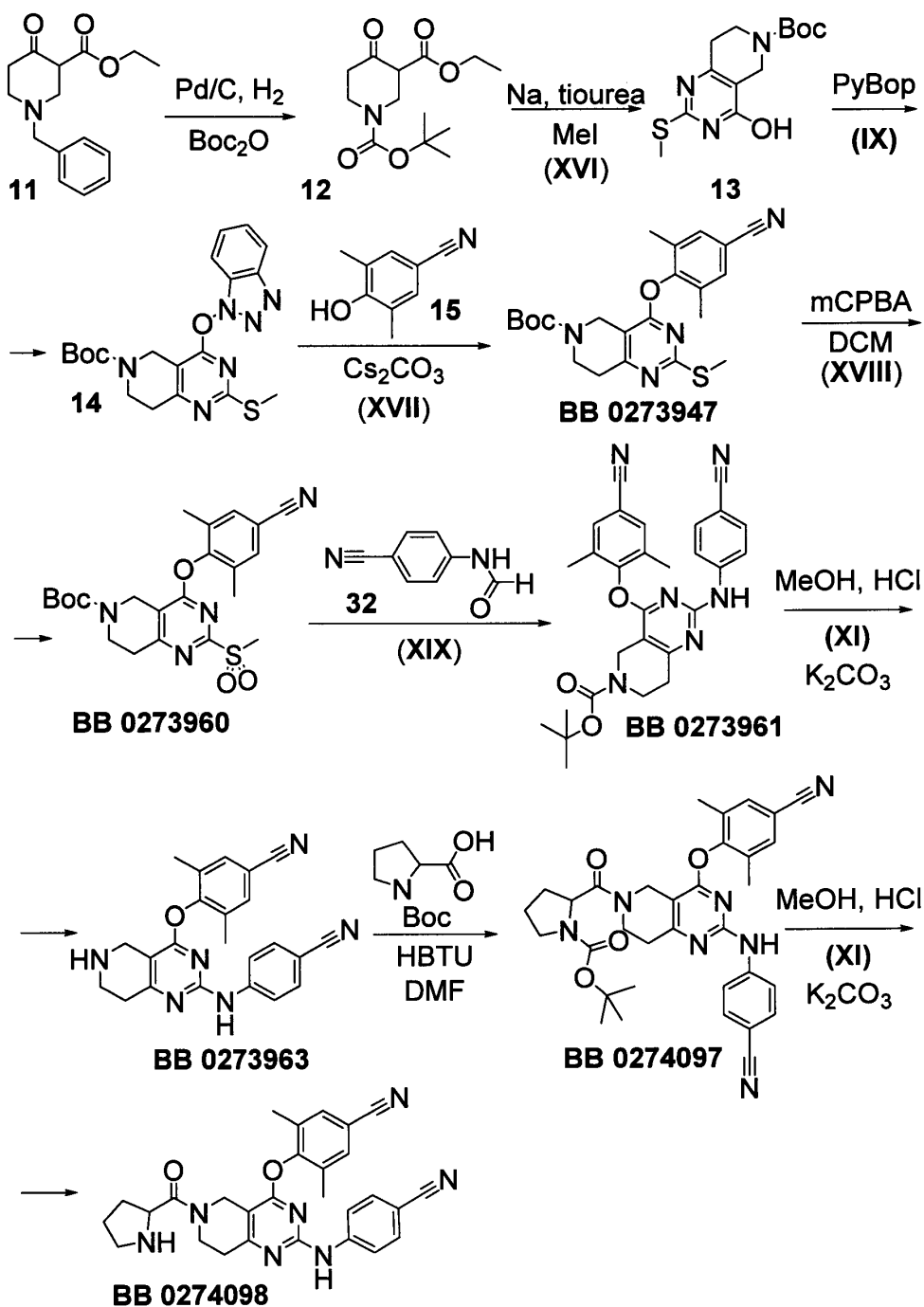
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Example 34.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(pyrrolidine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274098

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^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 1.91 (broadened singlet, 3H), 2.07 - 2.17

117

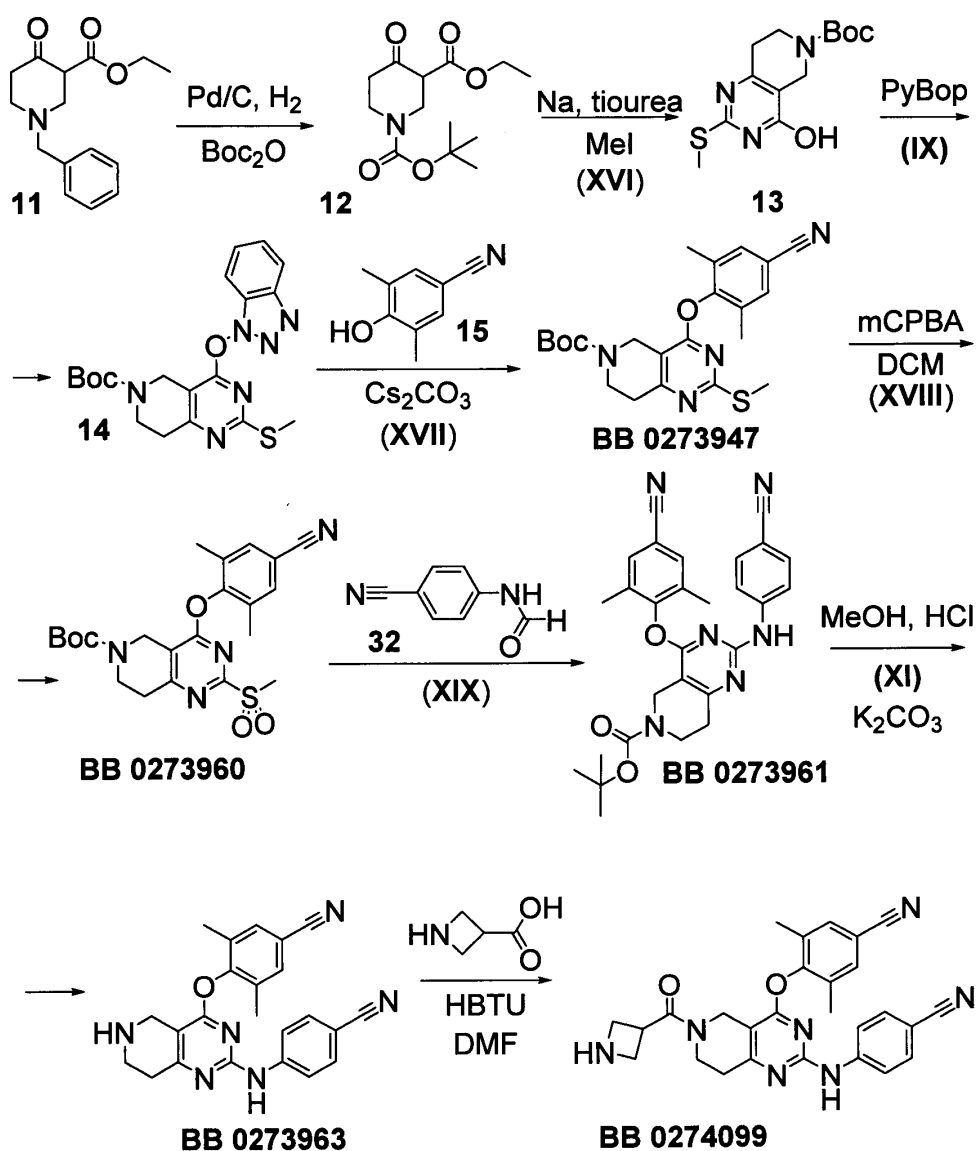
(m, 6H), 2.78 - 2.98 (m, 2H), 3.10 - 3.32 (m, 2H), 3.90 (broadened singlet, 2H), 4.50 - 4.85 (m, 3H), 7.46 (broadened singlet, 4H), 7.79 (s, 2 H), 8.35 - 8.63 (m, 1H), 10.12 (broadened singlet, 2 H).

Weight Yield - 0.032 g (88%)

5 LCMS m/z (M+H): 494

Example 35.

Synthesis of 4-((6-(azetidine-3-carbonyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



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BB 0274099

^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.10 (s, 6H), 2.73 - 2.91 (m, 2H), 3.00 - 3.56 (m, 1H), 3.65 (s, 2H), 4.05 - 4.09 (m, 2H), 4.25 - 4.31 (m, 2H), 4.68 (s, 2H), 7.46 (broadened singlet, 4H), 7.79 (s, 2H).

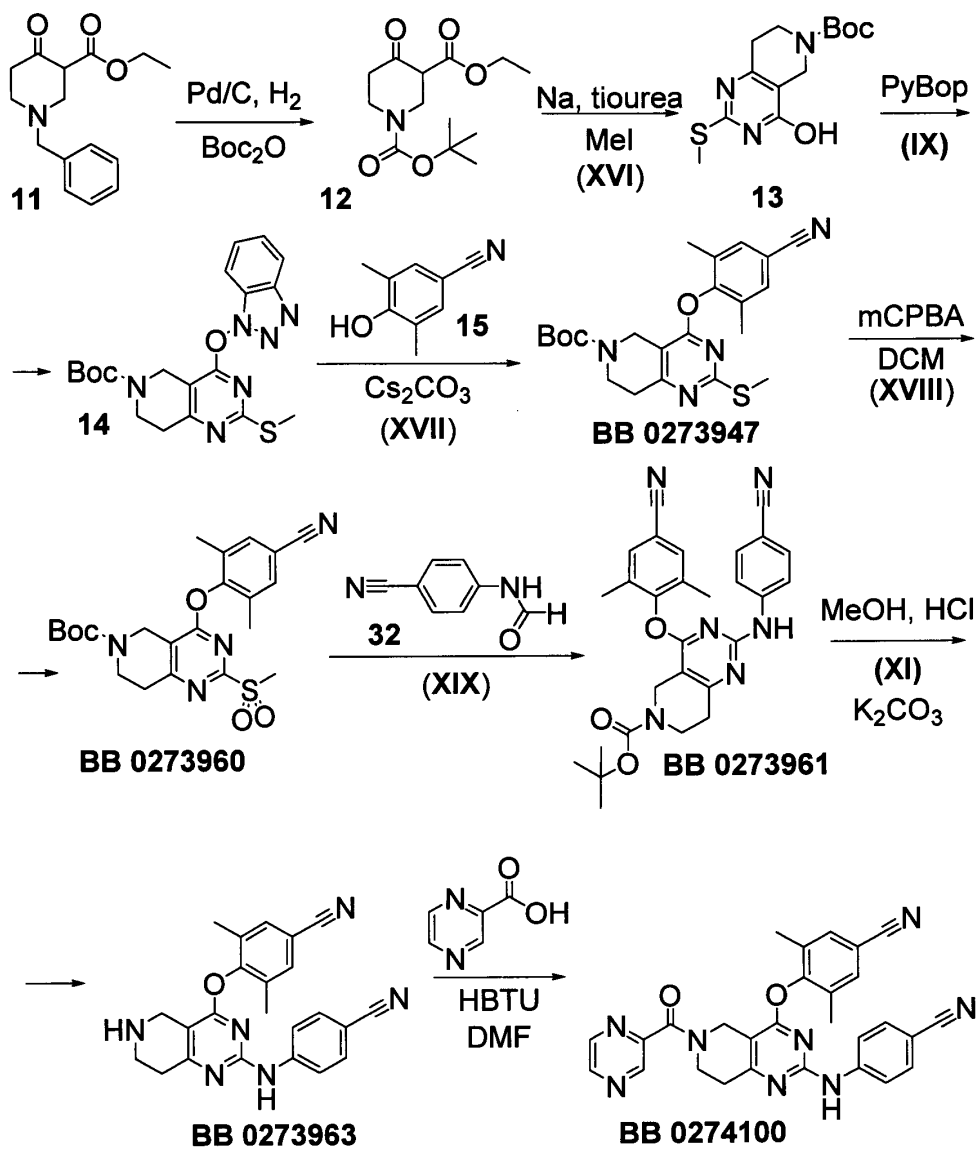
Weight Yield - 0.075 g (52%)

10

LCMS m/z (M+H): 480

Example 36.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(pyrazine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274100

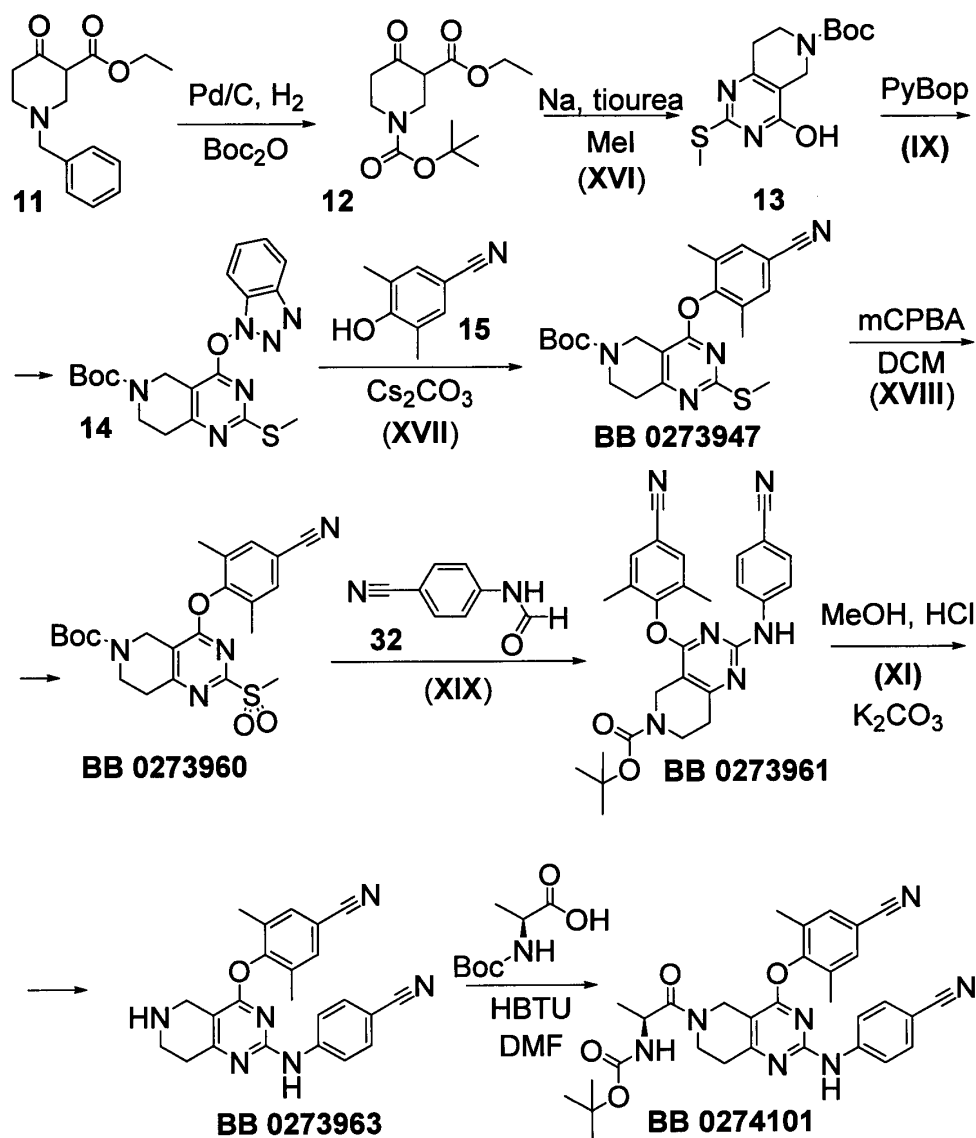
5 $^1\text{H NMR}$ (400 MHz, DMSO- d_6 , δ , ppm): 2.19 (s, 6H), 3.00 - 3.14 (m, 2H), 3.73 - 4.31 (m, 2H), 4.84 - 5.05 (m, 2H), 7.32 - 7.60 (m, 9H).

Weight Yield - 0.012 g (20%)

LCMS m/z (M+H): 503

Example 37.

Synthesis of (S)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxopropane-2-yl)carbamate



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BB 0274101

^1H NMR (400 MHz, DMSO-d_6 , δ , ppm): 1.35 - 1.49 (m, 9H), 1.61 (s, 3H), 2.17 (s, 6H), 2.55 - 2.86 (m, 1H), 3.07 (broadened singlet, 2H), 3.62 - 4.07 (m, 2H), 4.56 (s, 2H), 4.94 - 5.57 (m, 2H), 7.35 (broadened singlet, 2H), 7.39 - 7.44 (m, 2H), 7.48 (s, 2H).

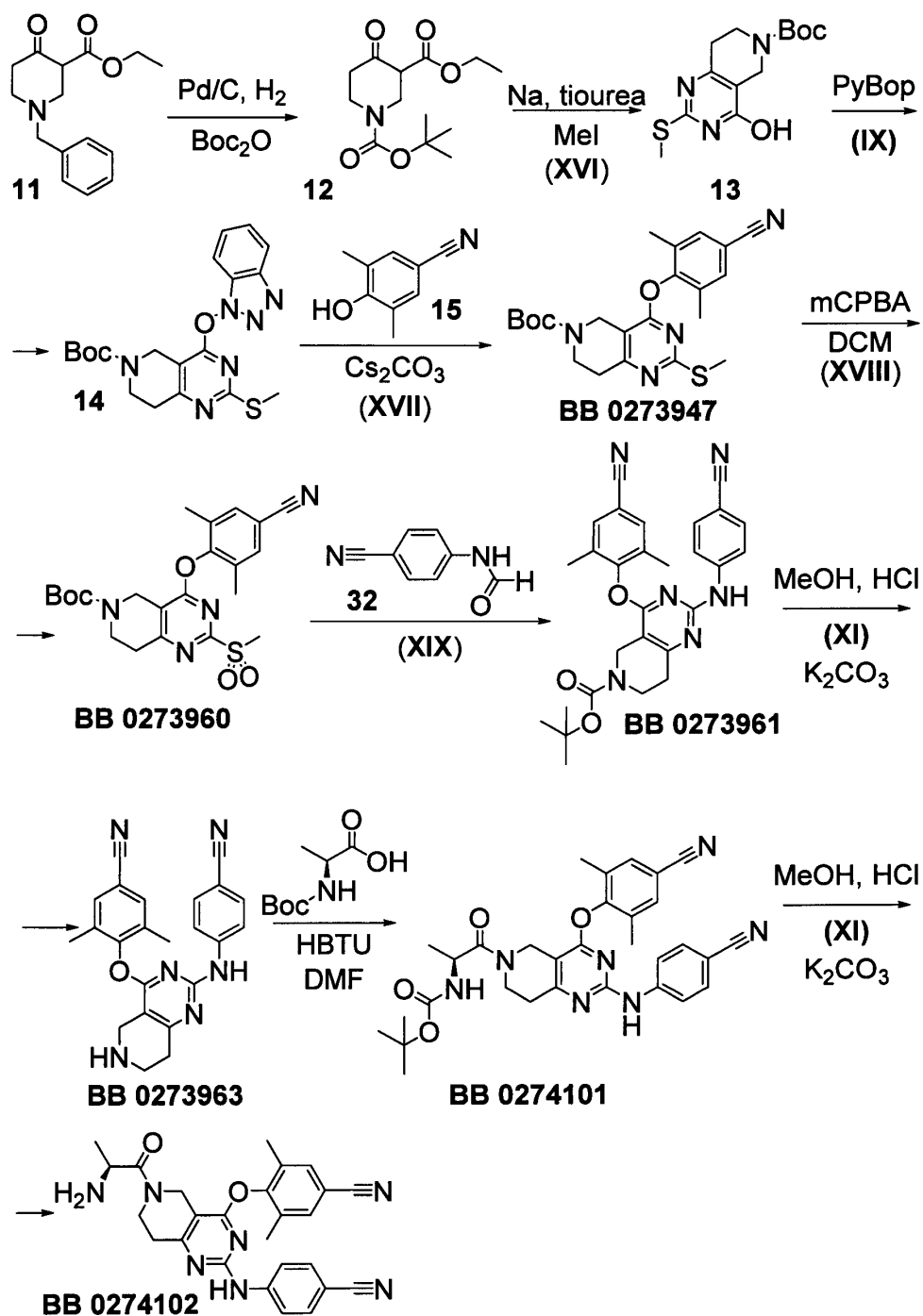
Weight Yield - 0.075 g (52%)

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LCMS m/z ($\text{M}+\text{H}$): 468 ($\text{M}-\text{Boc}$).

Example 38.

Synthesis of (S)-4-((6-(2-aminopropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274102

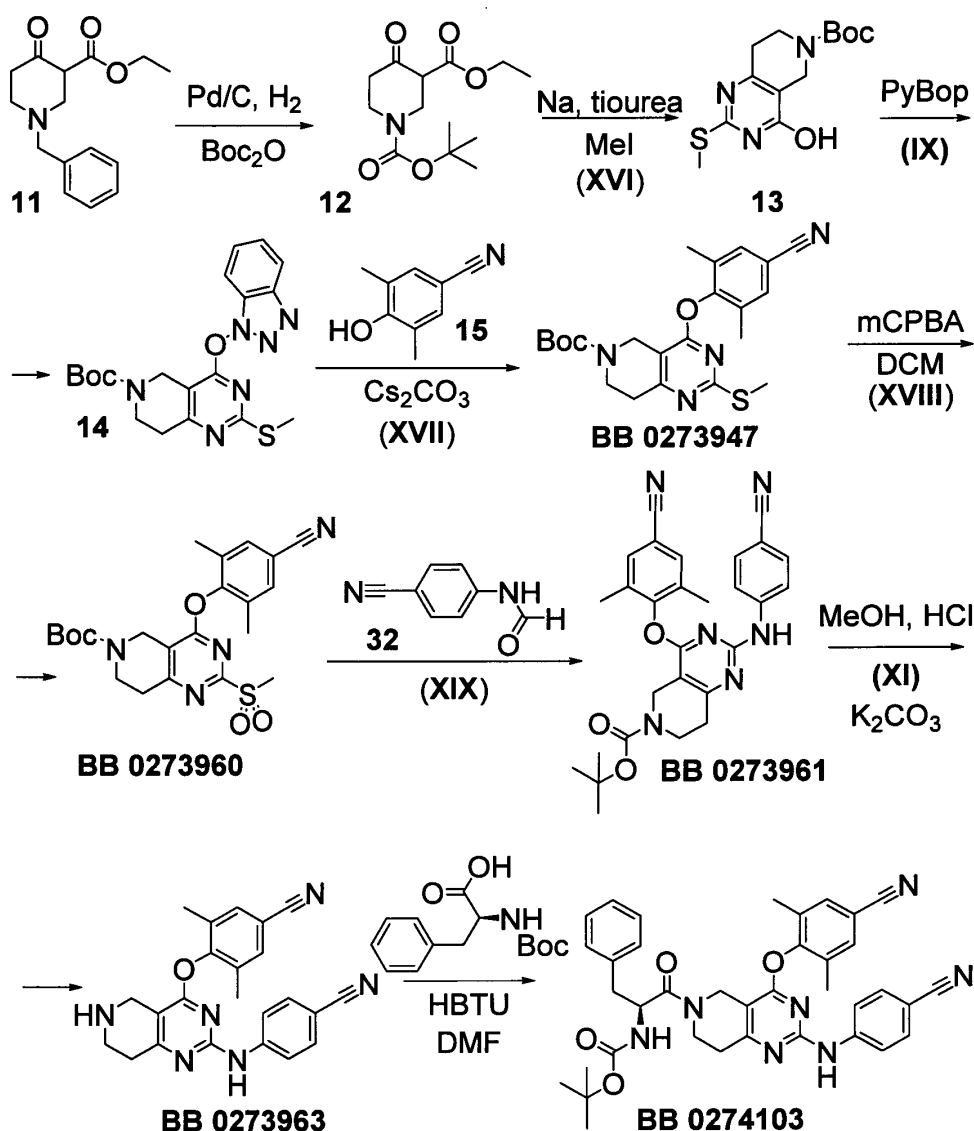
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.28 - 1.44 (m, 3H), 2.11 (s, 6H), 2.74 -
5 2.84 (m, 1H), 3.73 - 4.03 (m, 2H), 4.49 - 4.61 (m, 2H), 4.71 - 4.77 (m, 2H), 7.46
(broadened singlet, 4H), 7.79 (s, 2H), 7.94 (s, 1 H), 8.33 (broadened singlet, 2H).

Weight Yield - 0.0233 g (88%)

LCMS m/z (M+H): 468

Example 39.

Synthesis of (S)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxo-3-phenylpropane-2-yl)carbamate



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BB 0274103

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.41 - 1.51 (m, 9H), 2.15-2.20 (m, 6H), 2.83 - 2.96 (m, 2H), 3.38 - 4.01 (m, 6H), 4.47 - 4.96 (m, 4H), 6.90 - 7.14 (m, 2H), 7.41 (broadened singlet, 6H), 7.50 (m, 3H).

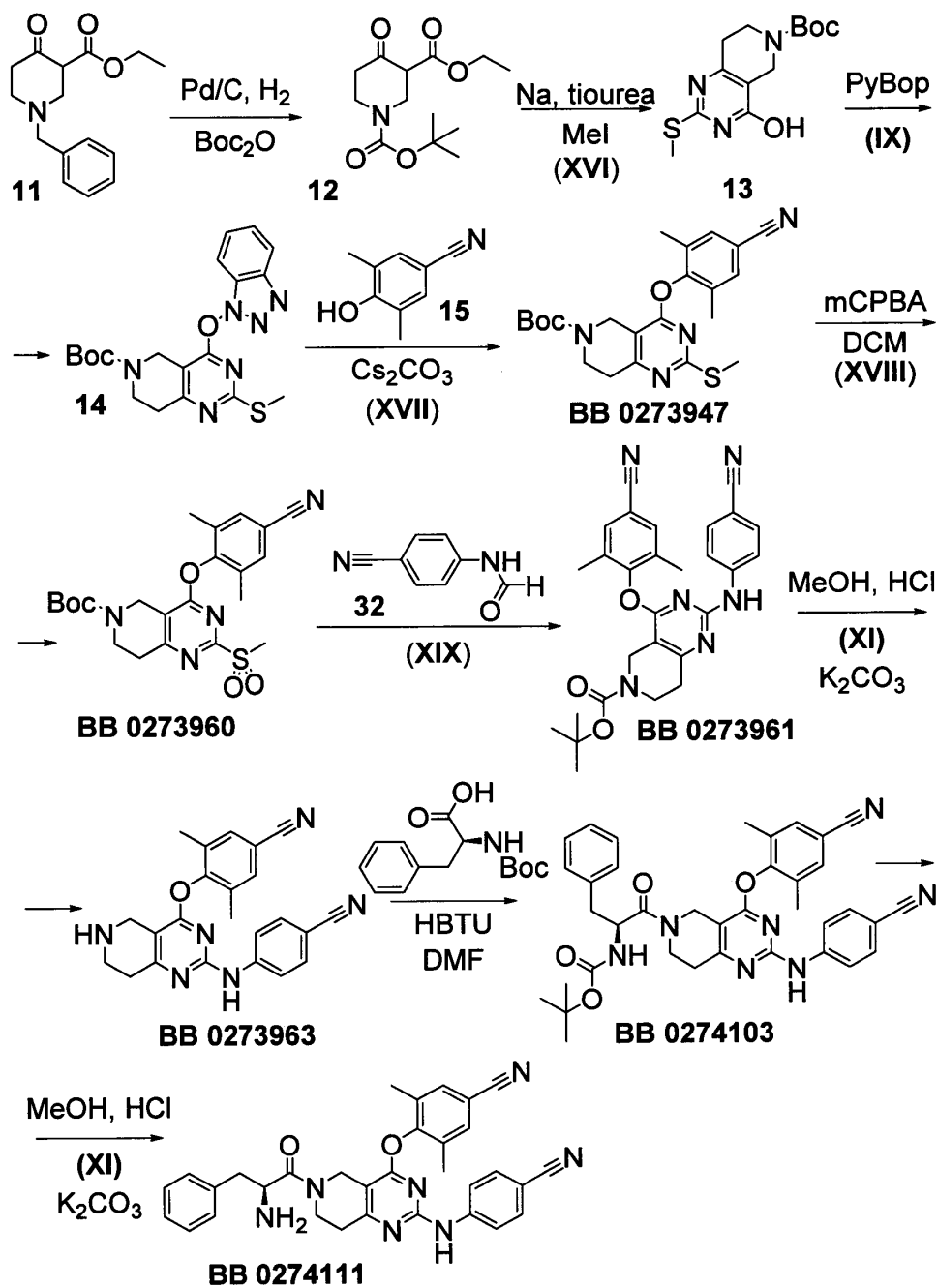
Weight Yield - 0.082 g (63%)

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LCMS m/z (M+H): 544 (M-Boc).

Example 40.

Synthesis of (S)-4-((6-(2-amino-3-phenylpropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274111

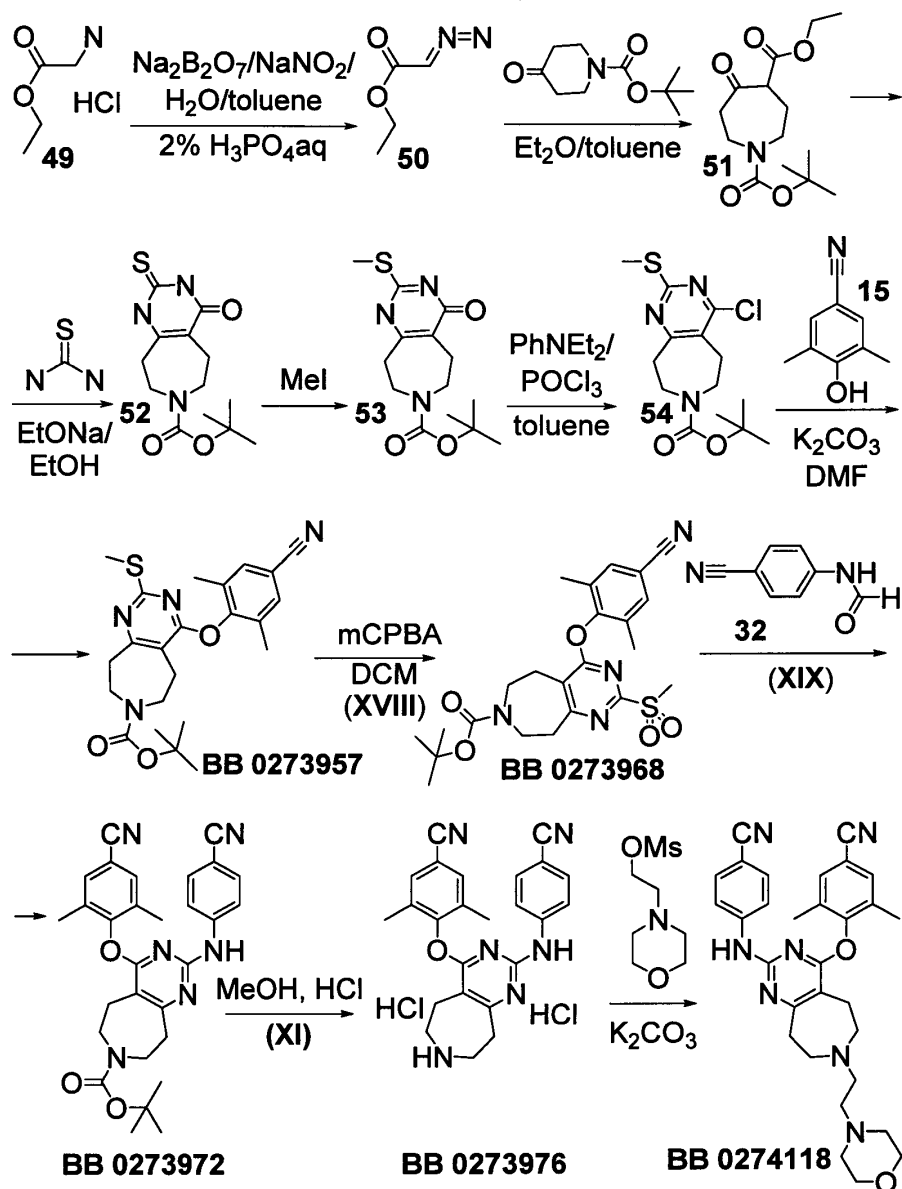
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.09 (broadened singlet, 6H), 2.59 - 2.82
5 (m, 1H), 3.15 (broadened singlet, 2H), 3.33 - 3.60 (m, 1H), 3.67 - 4.08 (m, 1H), 4.40 -
4.56 (m, 2H), 4.79 (broadened singlet, 2H), 7.26 (m, 5H), 7.43 (broadened singlet, 4H),
7.79 (broadened singlet, 2H), 8.46 (broadened singlet, 2H), 10.10 (broadened singlet,
1H).

Weight Yield - 0.078 g (86%)

10 LCMS m/z (M+H): 544

Example 41.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(2-morpholinoEthyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274118

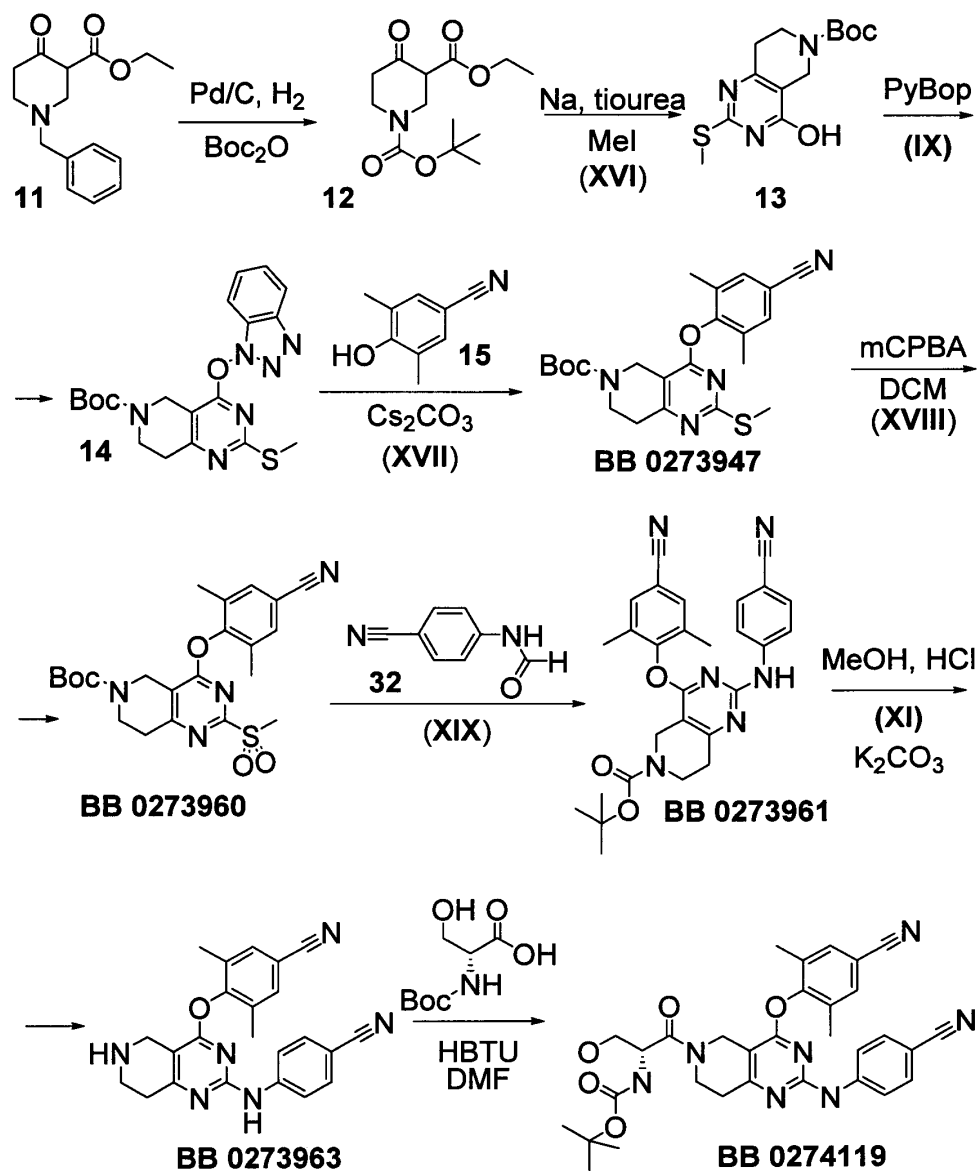
- 5 ^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.14 (s, 6H), 2.52 (broadened singlet, 4H), 2.58 (t, $J=6.90$ Hz, 2H), 2.70-2.86 (m, 6H), 3.00-3.12 (m, 4H), 3.73 (t, $J=4.5$, 4H), 7.09 (s, 1H), 7.28-7.33 (m, 2H), 7.34-7.40 (m, 2H), 7.48 (s, 2H).

Weight Yield - 0.014 g (24%)

LCMS m/z ($M+H$): 524

Example 42.

Synthesis of (R)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-hydroxy-1-oxopropane-2-yl)carbamate



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BB 0274119

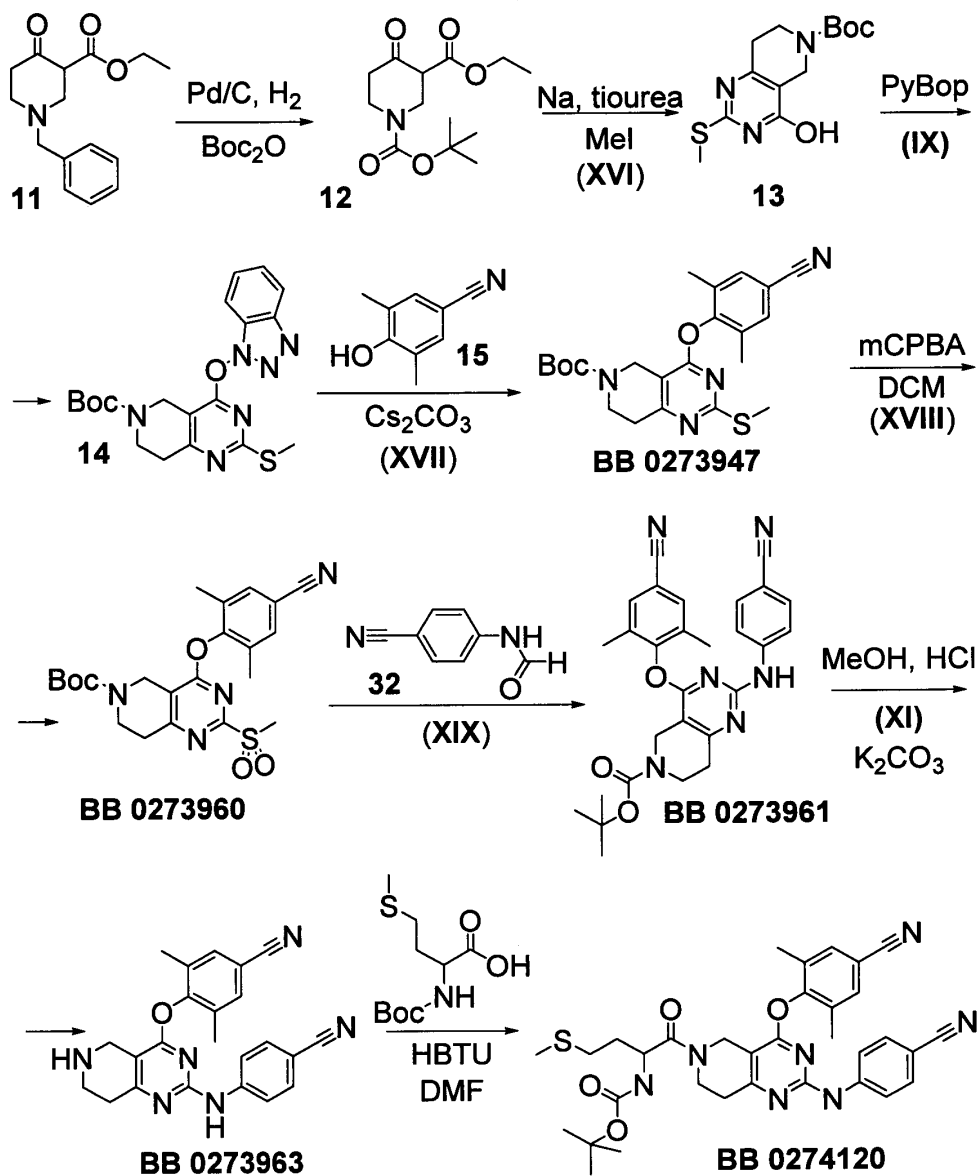
^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.45 (s, 9H), 2.17 (s, 6H), 3.71 - 4.17 (m, 4H), 4.59 - 5.03 (m, 3H), 5.37 - 5.77 (m, 1H), 7.31 - 7.45 (m, 4H), 7.49 (s, 2H).

Weight Yield - 0.011 g (42%)

LCMS m/z (M+H): 484 (M-Boc).

Example 43.

Synthesis of *tert*-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-(methylthio)-1-oxobutane-2-yl)carbamate



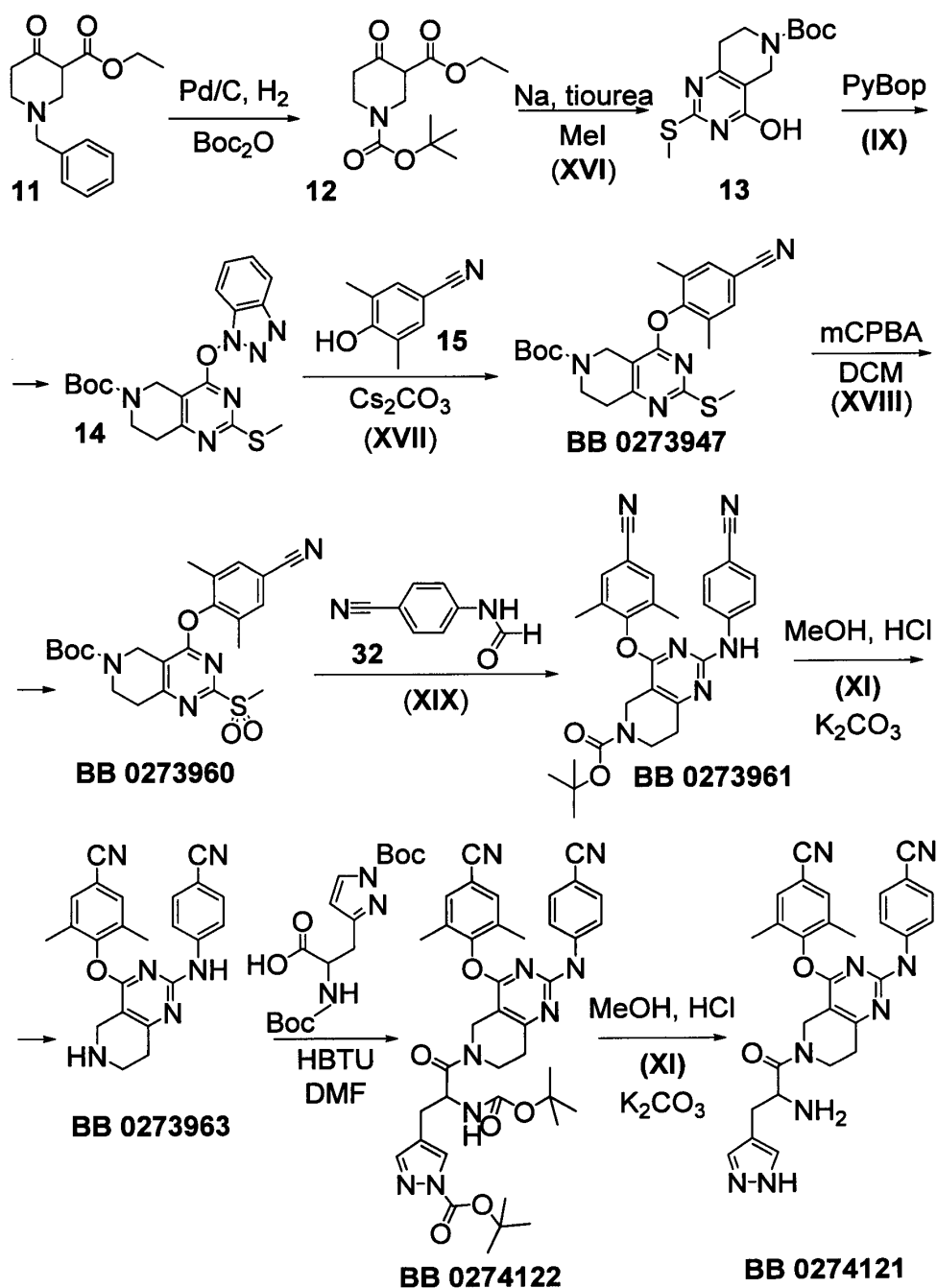
129

¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.43 (broadened singlet, 10H), 2.07 (s, 3H), 2.11 - 2.23 (m, 6H), 2.45 - 2.68 (m, 2H), 3.72 - 4.14 (m, 2H), 4.47 - 4.73 (m, 1H), 4.80 - 5.02 (m, 2H), 5.23 - 5.52 (m, 1H), 7.39 (d, *J*=4.6 Hz, 4 H), 7.48 (broadened singlet, 2H), 8.01 (s, 2 H).

- 5 Weight Yield - 0.089 g (55%)
 LCMS *m/z* (M+H): 528 (M-Boc)

Example 44.

Synthesis of 4-((6-(2-amino-3-(1H-pyrazole-4-yl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274121

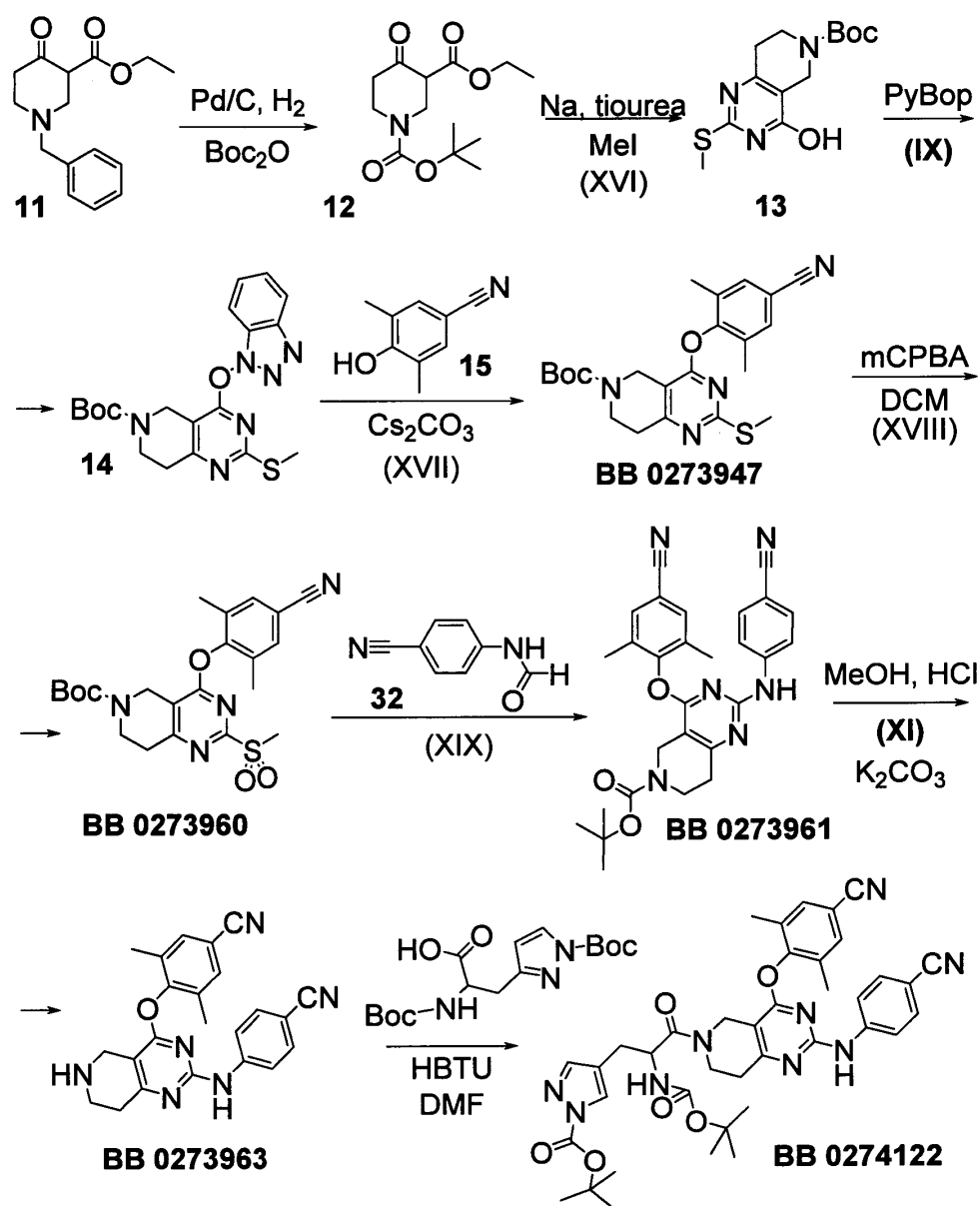
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.11 (broadened singlet, 6H), 2.60 - 3.01
5 (m, 2H), 3.05 - 3.42 (m, 2H), 3.84 - 4.29 (m, 3H), 4.51 - 4.64 (m, 1H), 4.77 - 5.00 (m, 2H),
7.46 (s, 4 H), 7.80 (s, 2H), 8.44 (broadened singlet, 2H), 9.13 (s, 1H), 10.05 (broadened
singlet, 1 H).

Weight Yield - 0.005 g (8%)

LCMS m/z (M+H): 534

Example 45.

Synthesis of *tert*-butyl 4-(2-((*tert*-butoxycarbonyl)amino)-3-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-*d*]pyrimidine-6(5H)-yl)-3-oxopropyl)-1H-pyrazole-1-carboxylate



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BB 0274122

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 1.36 - 1.48 (m, 9H), 1.50 - 1.65 (m, 9H), 2.15

133

(s, 6H), 3.02 - 3.21 (m, 1H), 3.61 - 3.95 (m, 1H), 4.01 - 4.28 (m, 1H), 4.45 - 4.69 (m, 1H), 4.75 - 4.84 (m, 1H), 4.88 - 5.01 (m, 1H), 5.04 - 5.18 (m, 1H), 5.42 - 5.58 (m, 1H), 7.14 (s, 1H), 7.20 (s, 1H), 7.35 - 7.44 (m, 4H), 7.48 (s, 2H).

Weight Yield - 0.032 g (33%)

5 LCMS m/z (M+H): 534 (M-2Boc)

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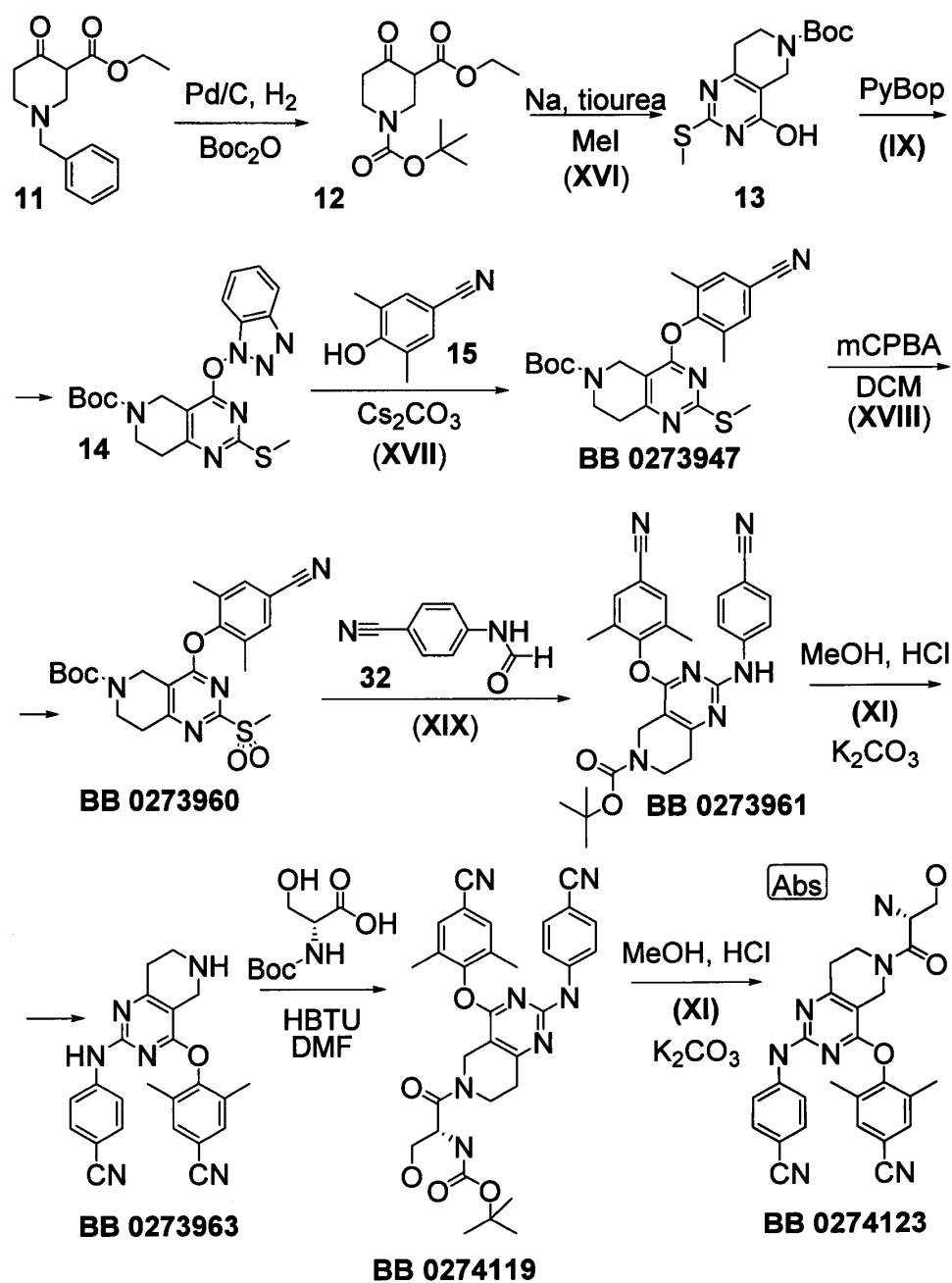
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Example 46.

Synthesis of (R)-4-((6-(2-amino-3-hydroxypropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274123

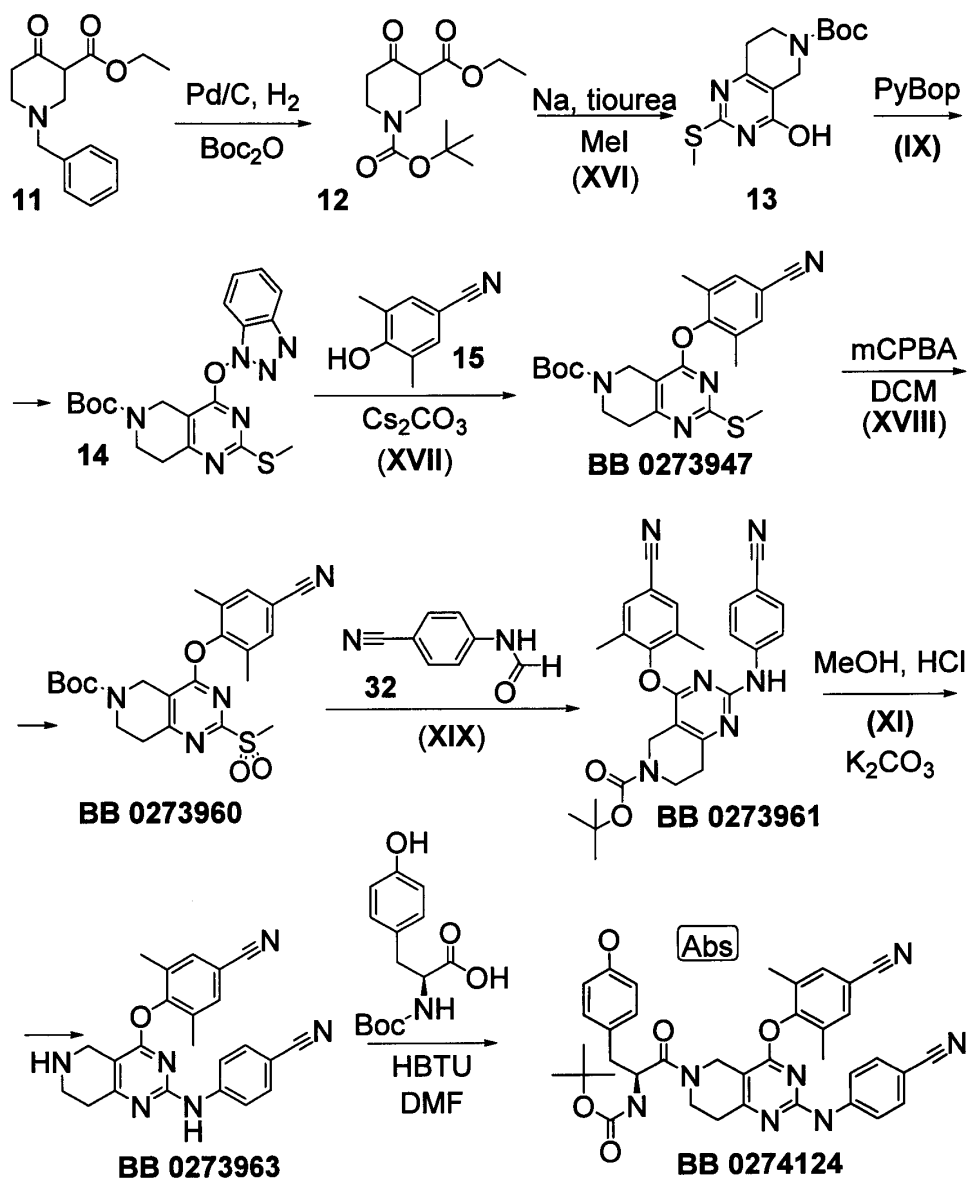
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.13 (s, 6H), 2.71 - 3.01 (m, 2H), 3.74 (broadened singlet, 2H), 3.95 (broadened singlet, 2H), 4.52 - 4.68 (m, 2H), 4.80 (broadened singlet, 2H), 7.46 (broadened singlet, 4H), 7.79 (s, 2 H), 8.30 (broadened singlet, 3H).

Weight Yield - 0.008 g (85%)

LCMS m/z (M+H): 484

Example 47.

Synthesis of (S)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-(4-hydroxyphenyl)-1-oxopropane-2-yl)carbamate

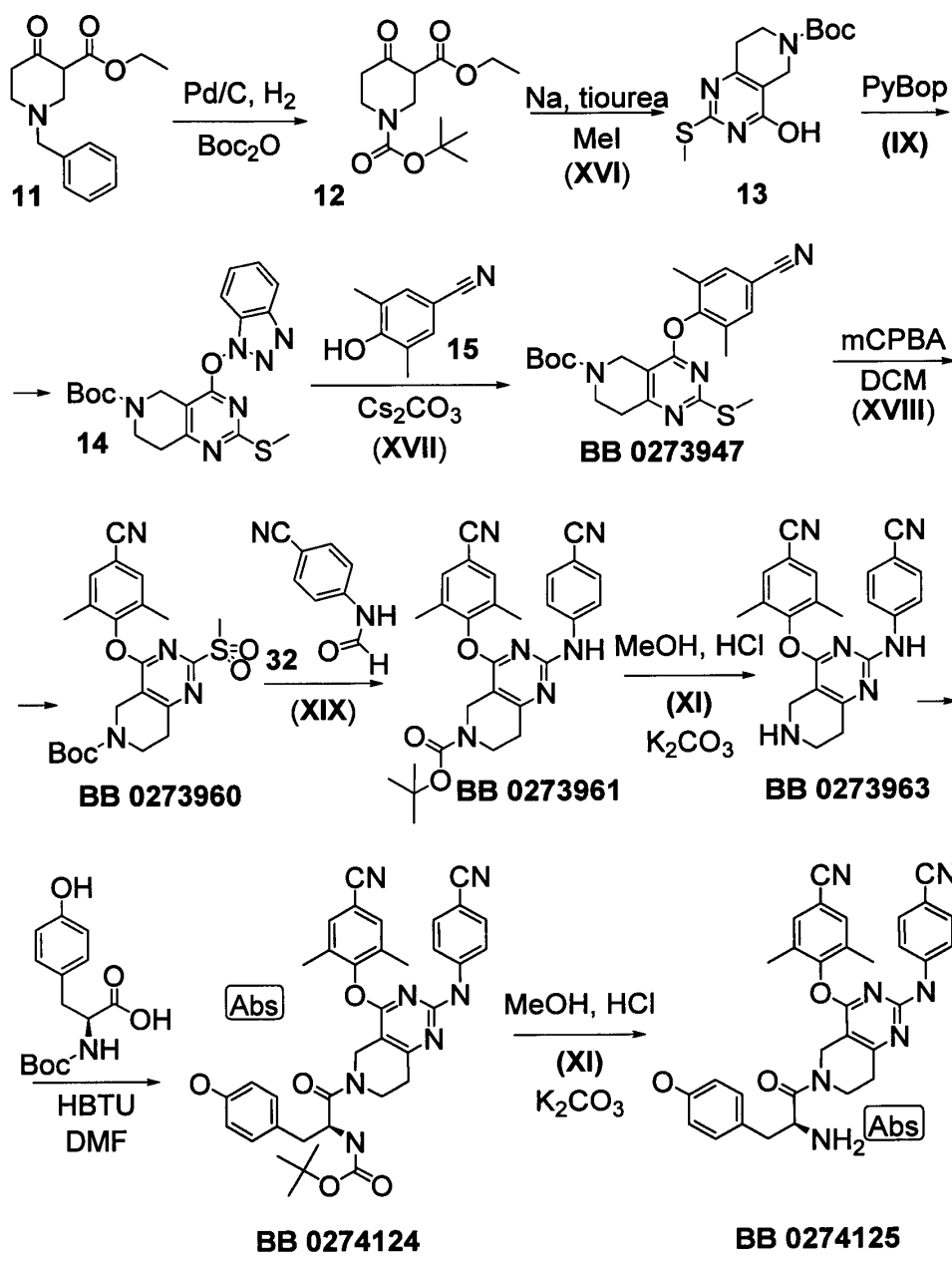


¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.43 (d, *J*=6.9 Hz, 9H), 2.17 (broadened singlet, 6H), 2.61 - 2.85 (m, 2H), 3.03 - 3.45 (m, 1H), 3.56 - 3.80 (m, 1H), 3.92 - 4.22 (m, 1H), 4.37 - 4.64 (m, 1H), 4.69 - 5.02 (m, 2H), 5.36 - 5.53 (m, 1H), 6.59 - 6.75 (m, 2H), 6.97 - 7.10 (m, 2H), 7.35 (d, *J*=15.5 Hz, 4H), 7.48 (s, 2 H).

5 Weight Yield - 0.055 g (40%)
 LCMS *m/z* (M+H): 560 (M-Boc).

Example 48.

Synthesis of (S)-4-((6-(2-amino-3-(4-hydroxyphenyl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274125

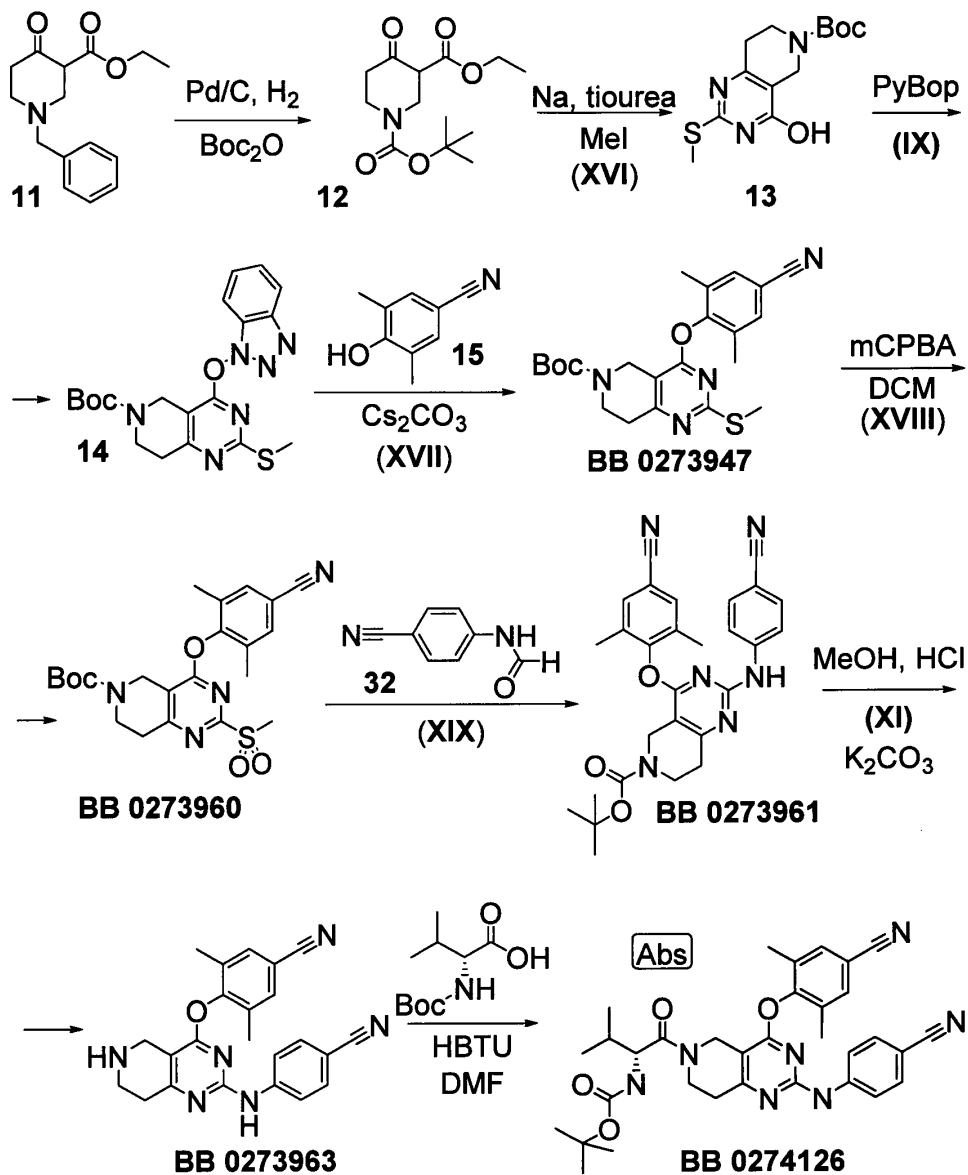
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.09 (broadened singlet, 6H), 2.59 - 2.82 (m, 1H), 3.15 (broadened singlet, 2H), 3.33 - 3.60 (m, 1H), 3.67 - 4.08 (m, 1H), 4.40 - 4.56 (m, 2H), 4.79 (broadened singlet, 2H), 7.26 (m, 5H), 7.43 (broadened singlet, 4H), 7.79 (broadened singlet, 2H), 8.46 (broadened singlet, 2H), 10.10 (broadened singlet, 1H).

Weight Yield - 0.048 g (90%)

LCMS m/z (M+H): 560

Example 49.

Synthesis of (R)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-methyl-1-oxobutane-2-yl)carbamate



BB 0274126

141

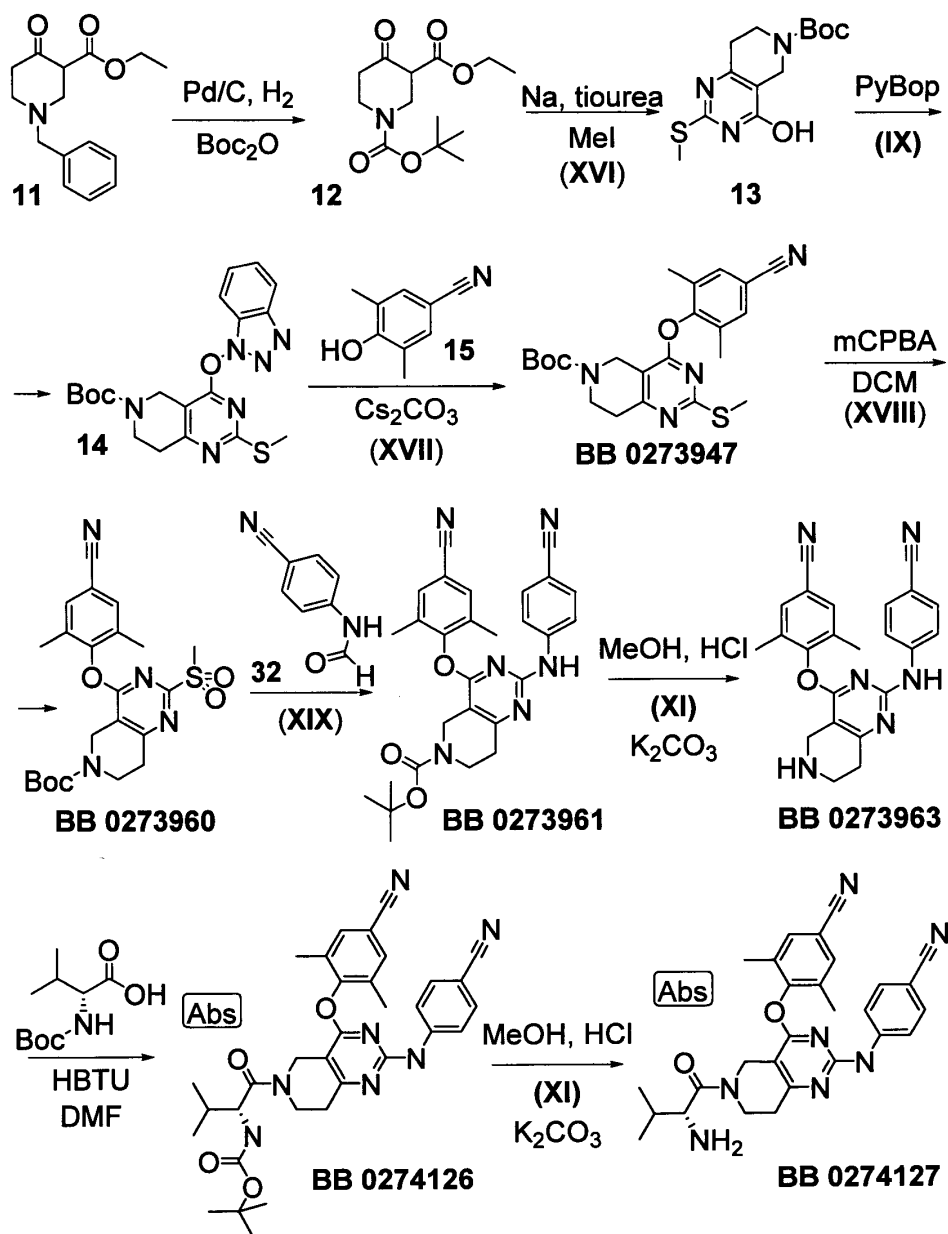
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 0.90 - 1.07 (m, 6H), 1.38 - 1.47 (m, 9H), 1.79 - 2.08 (m, 1H), 2.12 - 2.25 (m, 6H), 2.98 - 3.27 (m, 1H), 3.76 - 4.07 (m, 2H), 4.44 - 4.73 (m, 2H), 5.22 - 5.53 (m, 1H), 7.33 - 7.44 (m, 4H), 7.48 (s, 2H).

Weight Yield - 0.042 g (52%)

5 LCMS m/z (M+H): 496 (M-Boc).

Example 50.

Synthesis of (R)-4-((6-(2-amino-3-methylbutanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



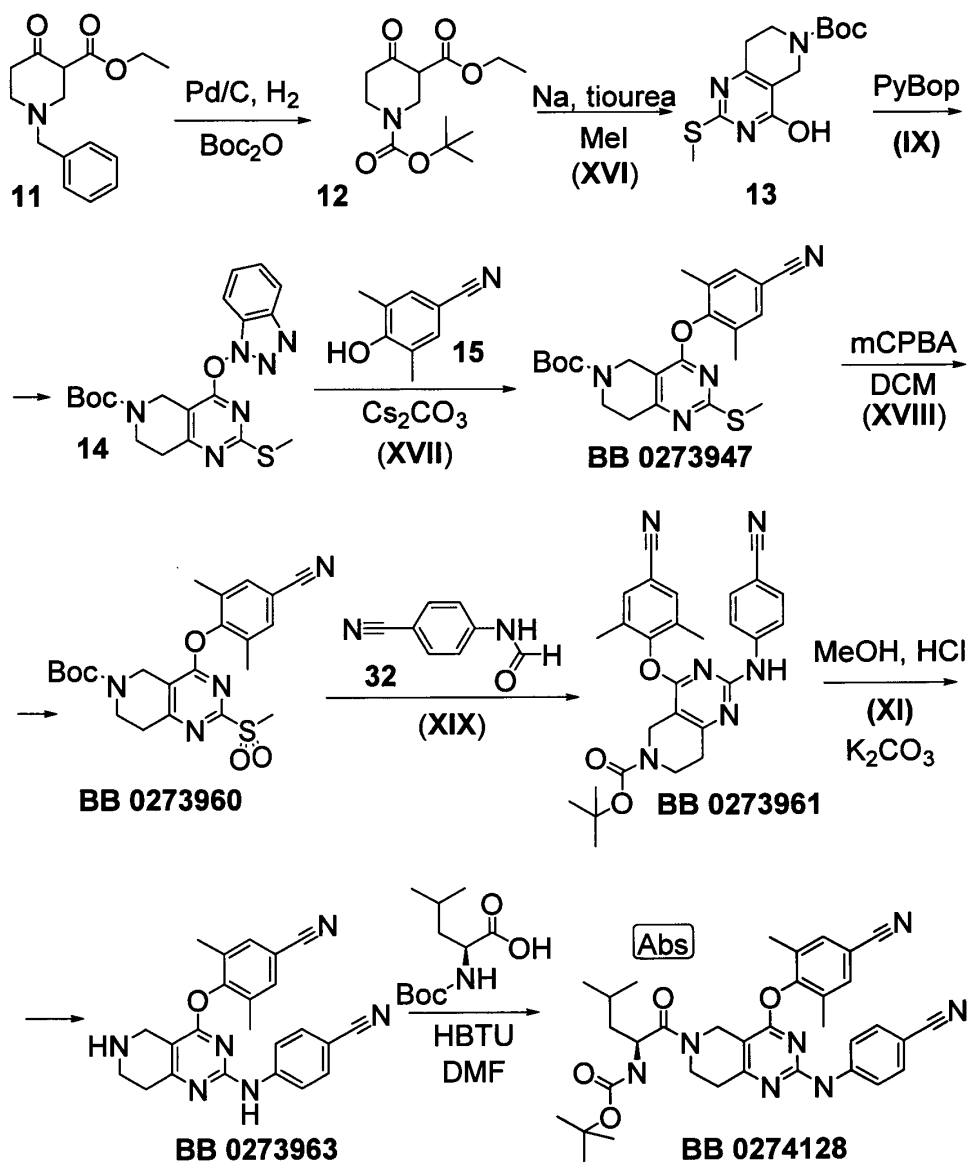
¹H NMR (400 MHz, CDCl₃, δ, ppm): 1.36 - 1.48 (m, 2H), 1.53 - 1.86 (m, 4H), 2.08 - 2.22 (s, 6H), 3.02 - 3.29 (m, 2H), 3.75 - 4.08 (m, 2H), 4.51 - 5.06 (m, 4H), 5.30 (s, 1H), 7.31 - 7.45 (m, 4H), 7.48 (s, 2 H).

5 Weight Yield - 0.038 g (92%)

LCMS m/z (M+H): 496

Example 51.

Synthesis of (S)-tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-methyl-1-oxopentane-2-yl)carbamate



5

BB 0274128

$^1\text{H NMR}$ (400 MHz, CDCl_3 , δ , ppm): 0.88 - 1.13 (m, 6H), 1.35 - 1.48 (m, 9H), 1.58

145

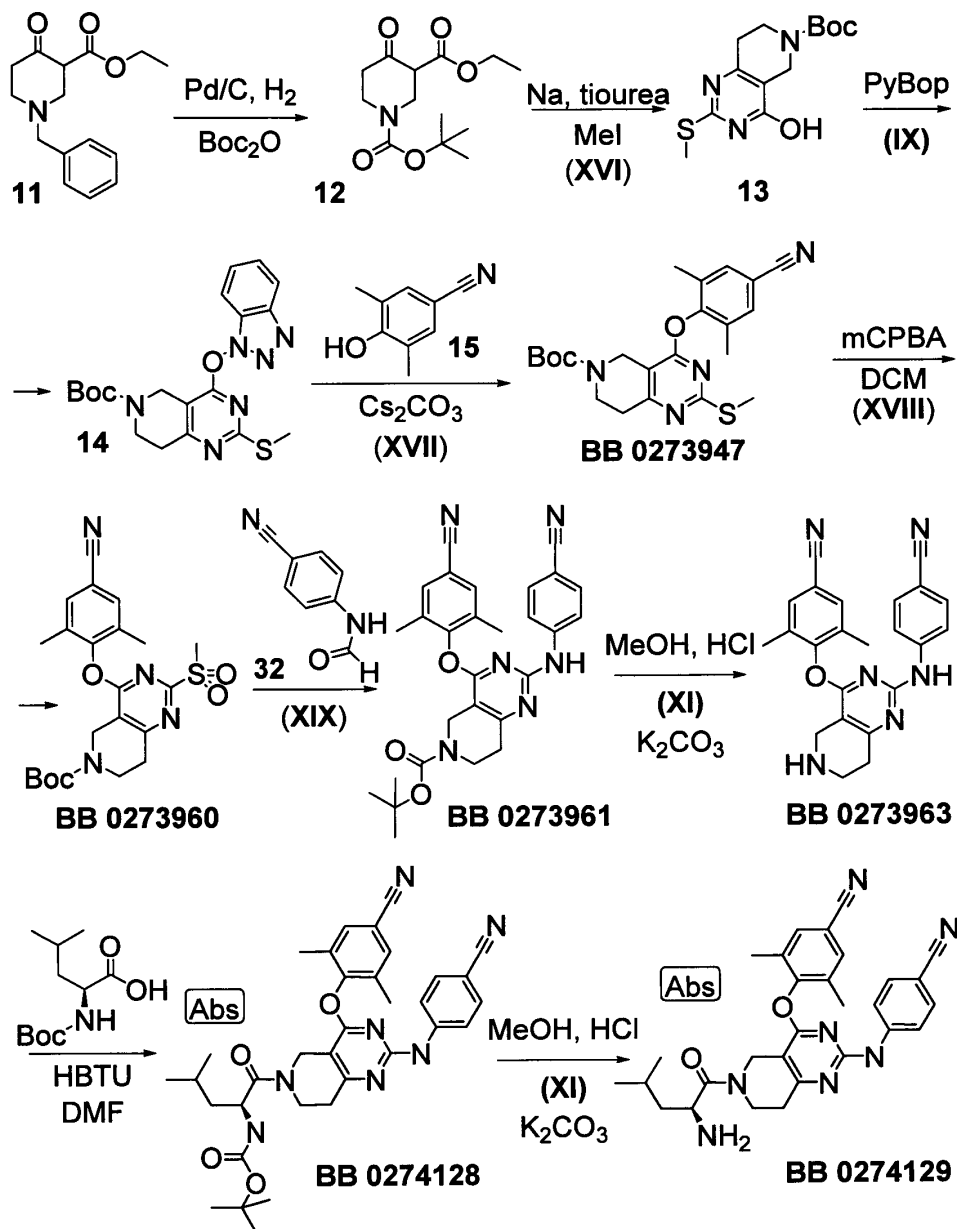
(d, $J=1.4$ Hz, 2H), 2.16 (s, 6H), 2.99 - 3.26 (m, 1H), 3.72 - 4.27 (m, 2H), 4.64 - 4.98 (m, 3H), 5.30 (s, 1 H), 7.33 - 7.45 (m, 4H), 7.45 - 7.56 (m, 2 H).

Weight Yield - 0.064 g (56%)

LCMS m/z (M+H): 510 (M-Boc

Example 52.

Synthesis of (S)-4-((6-(2-amino-4-methylpentanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



147

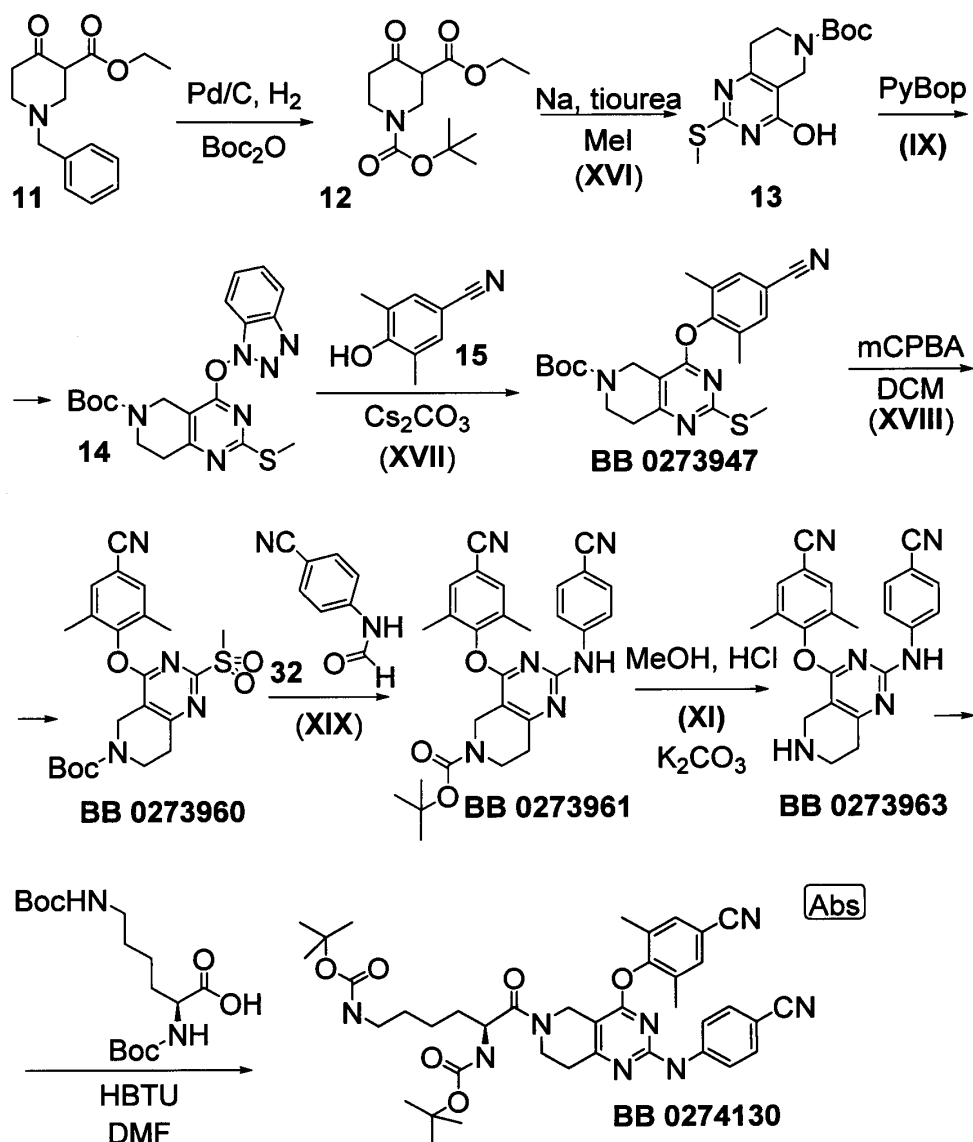
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 0.82 - 0.99 (m, 6H), 1.49 - 1.86 (m, 3H), 2.12 (s, 6H), 2.71 - 3.11 (m, 2H), 3.65 - 4.11 (m, 2H), 4.70 (s, 2H), 7.46 (broadened singlet, 4H), 7.79 (s, 2H), 8.28 (broadened singlet, 2H)

Weight Yield - 0.060 g (90%)

5 LCMS m/z (M+H): 510

Example 53.

Synthesis of (S)-di-tert-butyl (6-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-6-oxohexane-1,5-diyl)dicarbamate



5

BB 0274130

^1H NMR (400 MHz, DMSO-d_6 , δ , ppm): 1.22 - 1.76 (m, 22H), 1.70 - 1.87 (m, 2H), 2.13 (s, 6H), 2.62 - 2.80 (m, 2H), 2.84 - 3.12 (m, 2H), 3.75 - 3.88 (m, 2H), 4.50 - 4.60 (m, 2H), 7.46 (broadened singlet, 4H), 7.80 (s, 2H), 8.02 - 8.14 (m, 2H), 8.34-8.38 (m, 3H).

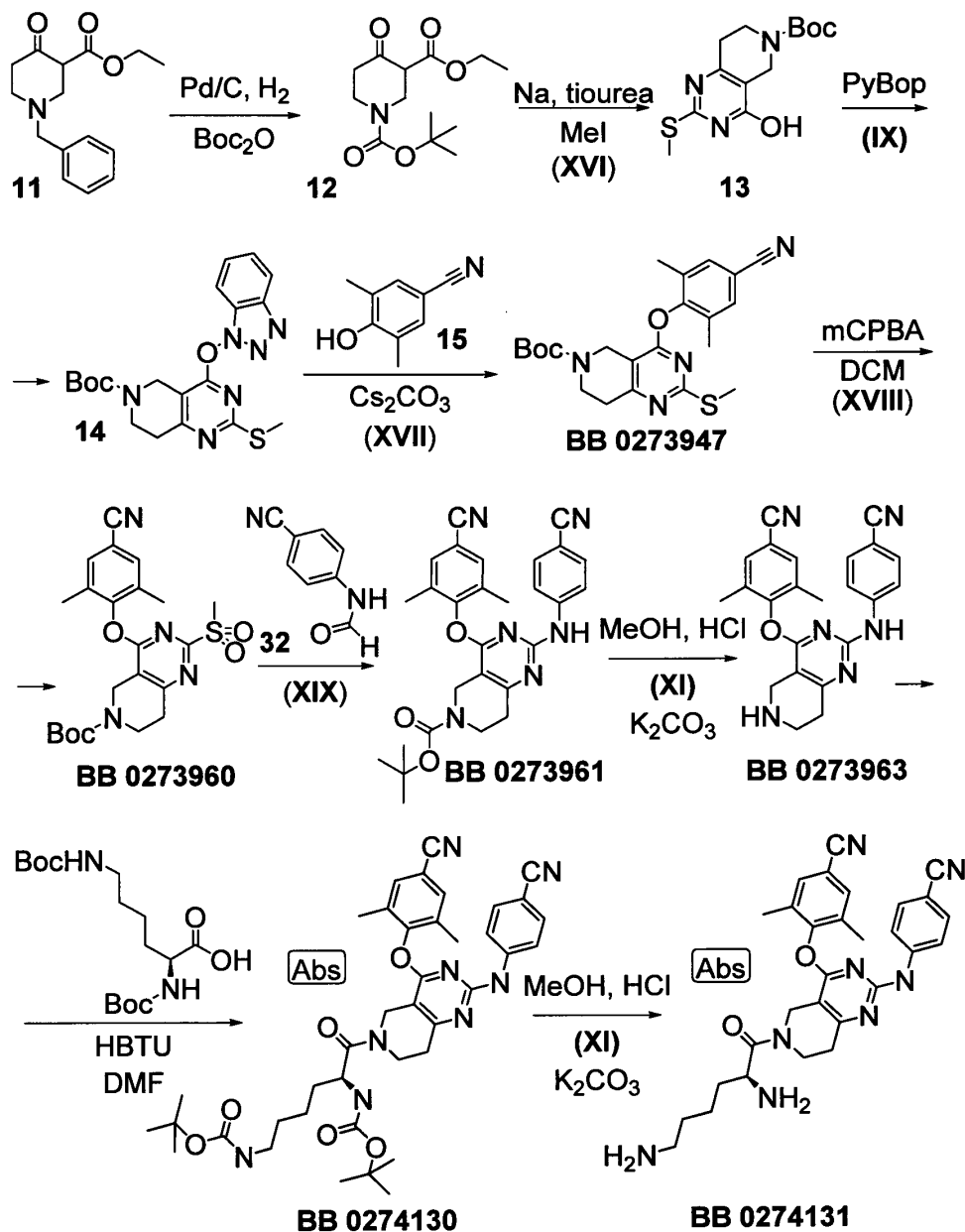
Weight Yield - 0.022 g (18%)

10

LCMS m/z ($\text{M}+\text{H}$): 525 ($\text{M}-2\text{Boc}$)

Example 54.

Synthesis of (S)-4-((2-((4-cyanophenyl)amino)-6-(2,6-diaminohexanoyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274131

- 5 ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 1.30 - 1.66 (m, 4H), 1.71 - 1.85 (m, 2H), 2.12 (s, 6H), 2.63 - 2.79 (m, 2H), 2.85 - 3.09 (m, 2H), 3.77 - 4.04 (m, 2H), 4.53 - 4.59 (m, 2H), 7.46 (broadened singlet, 4H), 7.79 (s, 2H), 8.01 - 8.14 (m, 3H), 8.36-8.40 (m, 3H)

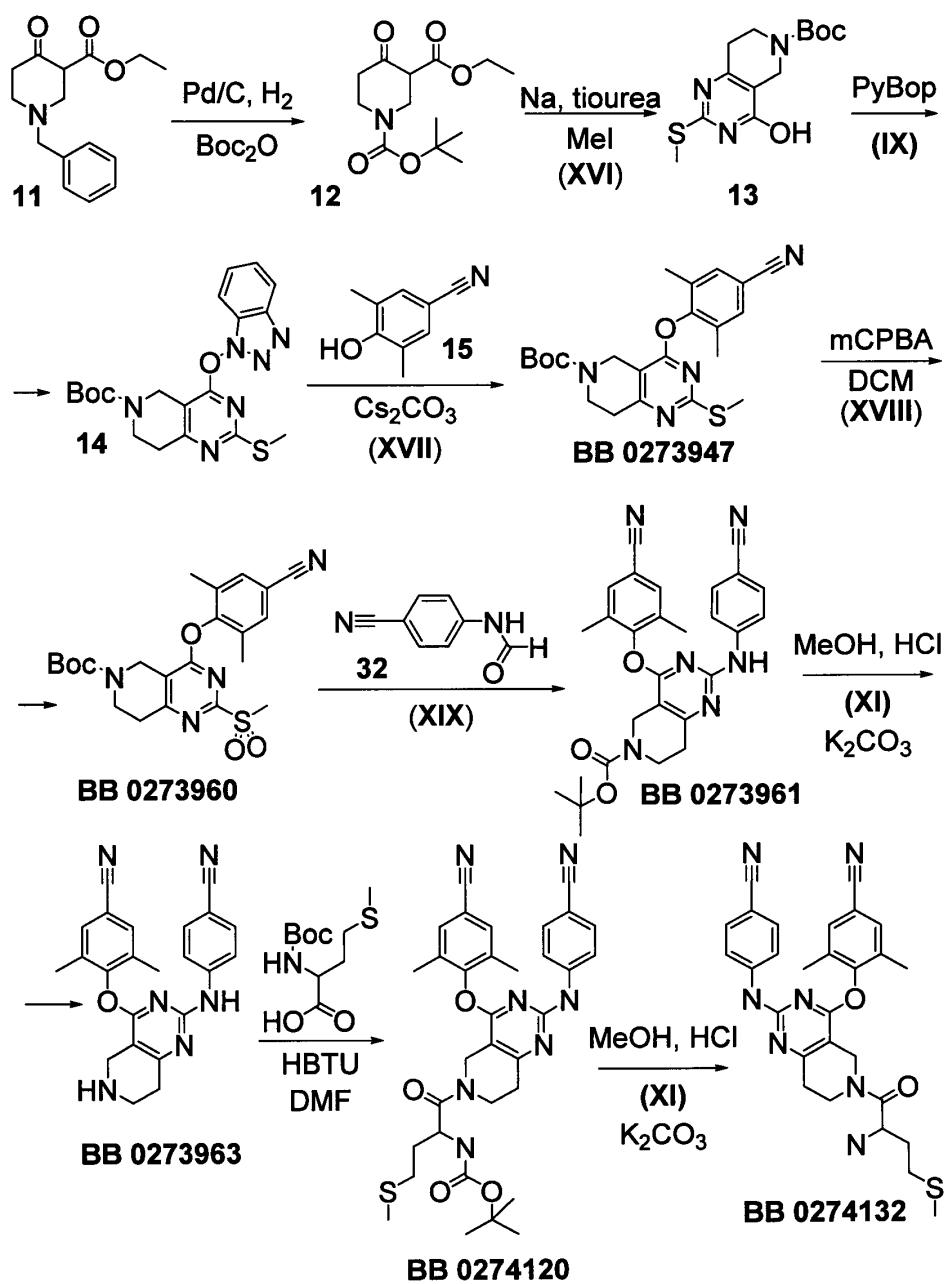
Weight Yield - 0.018 g (85%)

LCMS m/z (M+H): 525

Example 55.

Synthesis of (S)-4-((6-(2-amino-4-(methylthio)butanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

5



BB 0274132

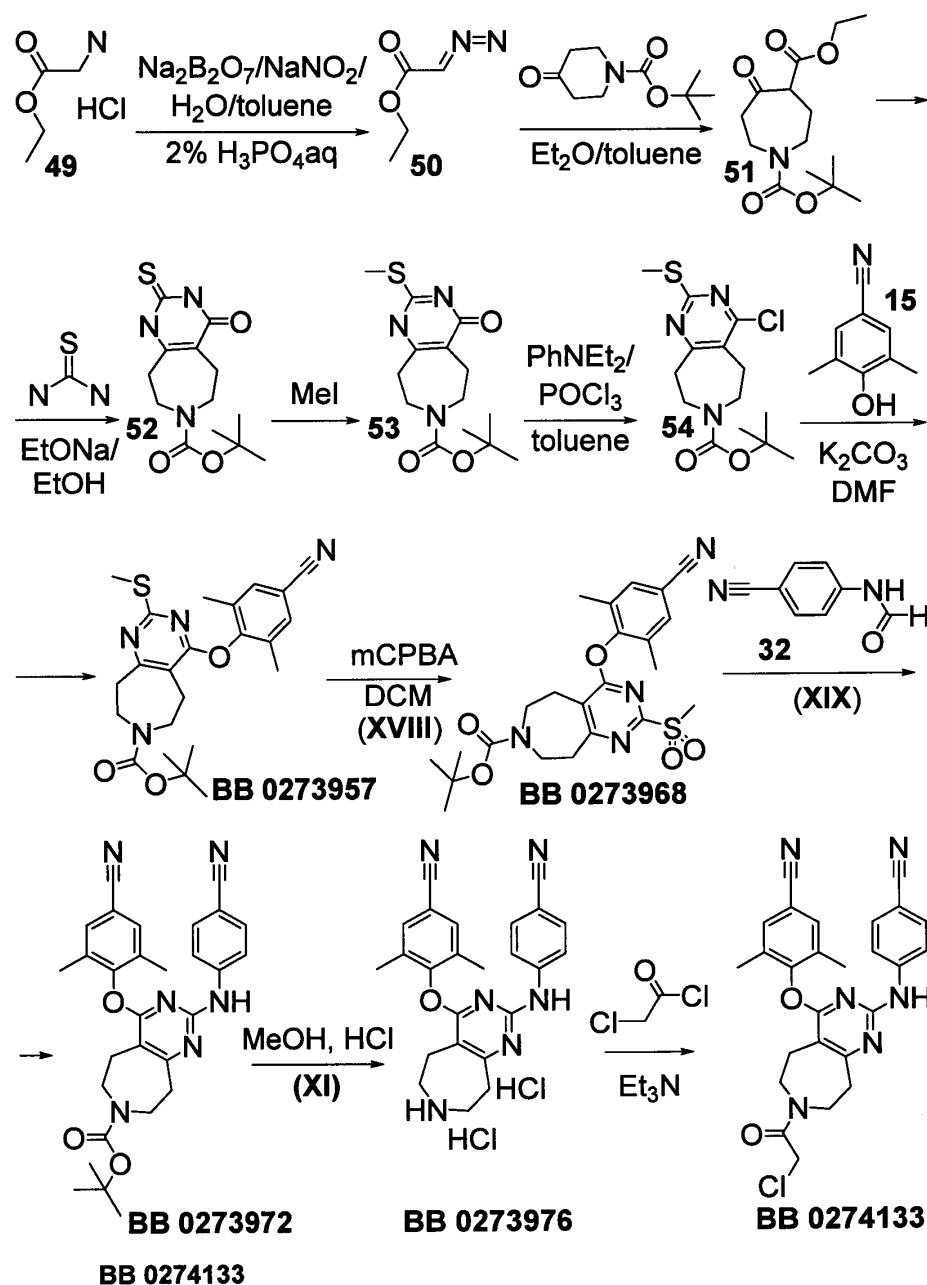
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.08 (s, 3H), 2.15 (broadened singlet, 6H),
2.51 - 2.73 (m, 2H), 2.80 - 3.07 (m, 2H), 3.79 - 4.08 (m, 2H), 4.47 - 4.57 (m, 2H), 4.81 -
5 5.01 (m, 2H), 7.46 (broadened singlet, 4H), 7.79 (s, 2H), 8.40 (broadened singlet, 2H)

Weight Yield - 0.076 g (82%)

LCMS m/z (M+H): 528

Example 56.

Synthesis of 4-((7-(2-chloroacetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



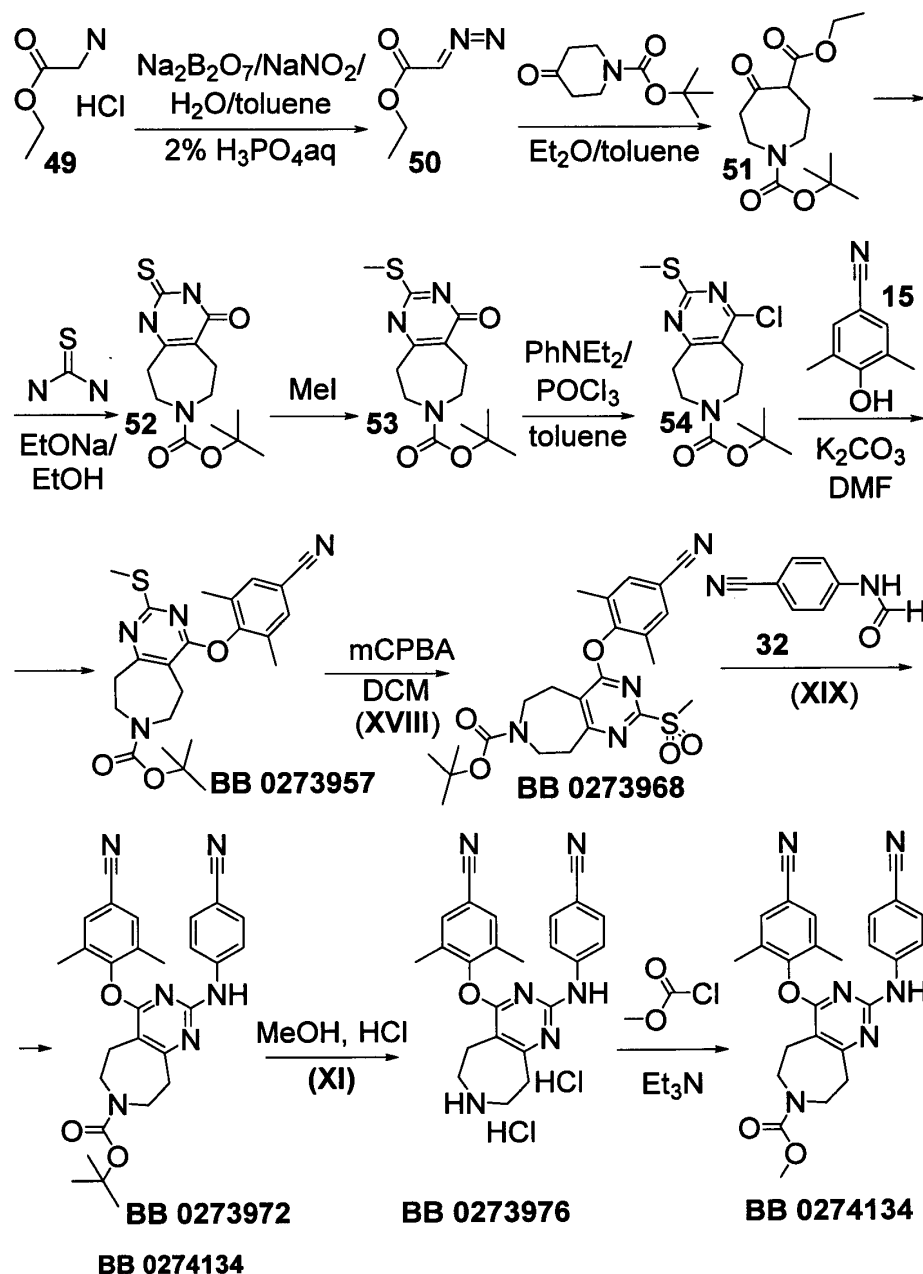
- 5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 2.10 (s, 6H), 3.02 (broadened singlet, 2H), 3.13 (broadened singlet, 2H), 3.75 (broadened singlet, 4H), 4.49 (broadened singlet, 2H), 7.42 (broadened singlet, 4H), 7.78 (broadened singlet, 2H), 10.06 (broadened singlet, 1H).

Weight Yield - 0.045 g (57%)

LCMS m/z (M+H): 487

Example 57.

Synthesis of methyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate



5

BB 0274134

 ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ , ppm): 2.09 (s, 6H), 3.03 (broadened singlet, 4H),

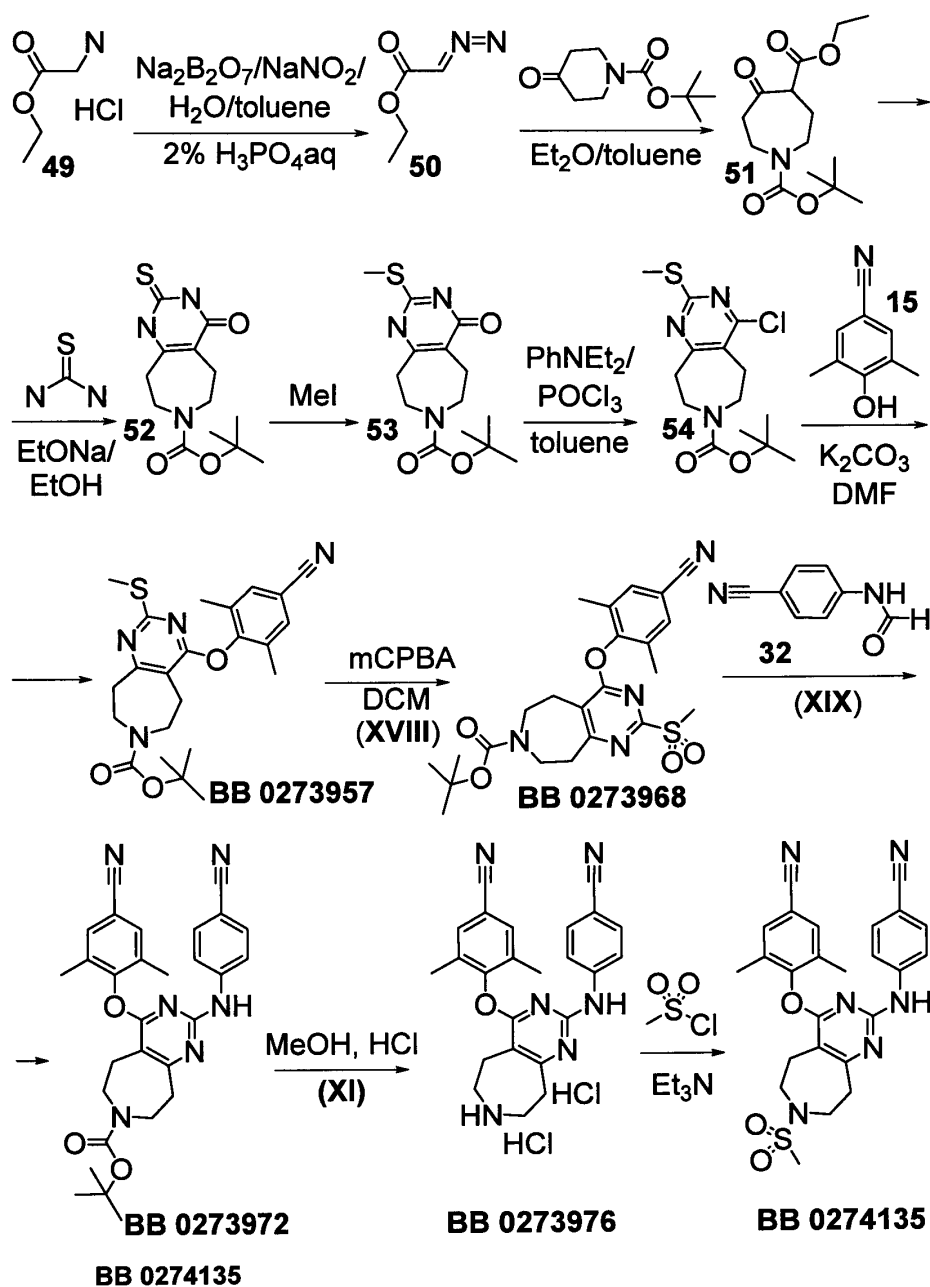
3.64 (s, 7H), 7.41 (s, 4H), 7.77 (s, 2H), 10.06 (s, 1H).

Weight Yield - 0.095 g (82%)

LCMS m/z (M+H): 469

Example 58.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



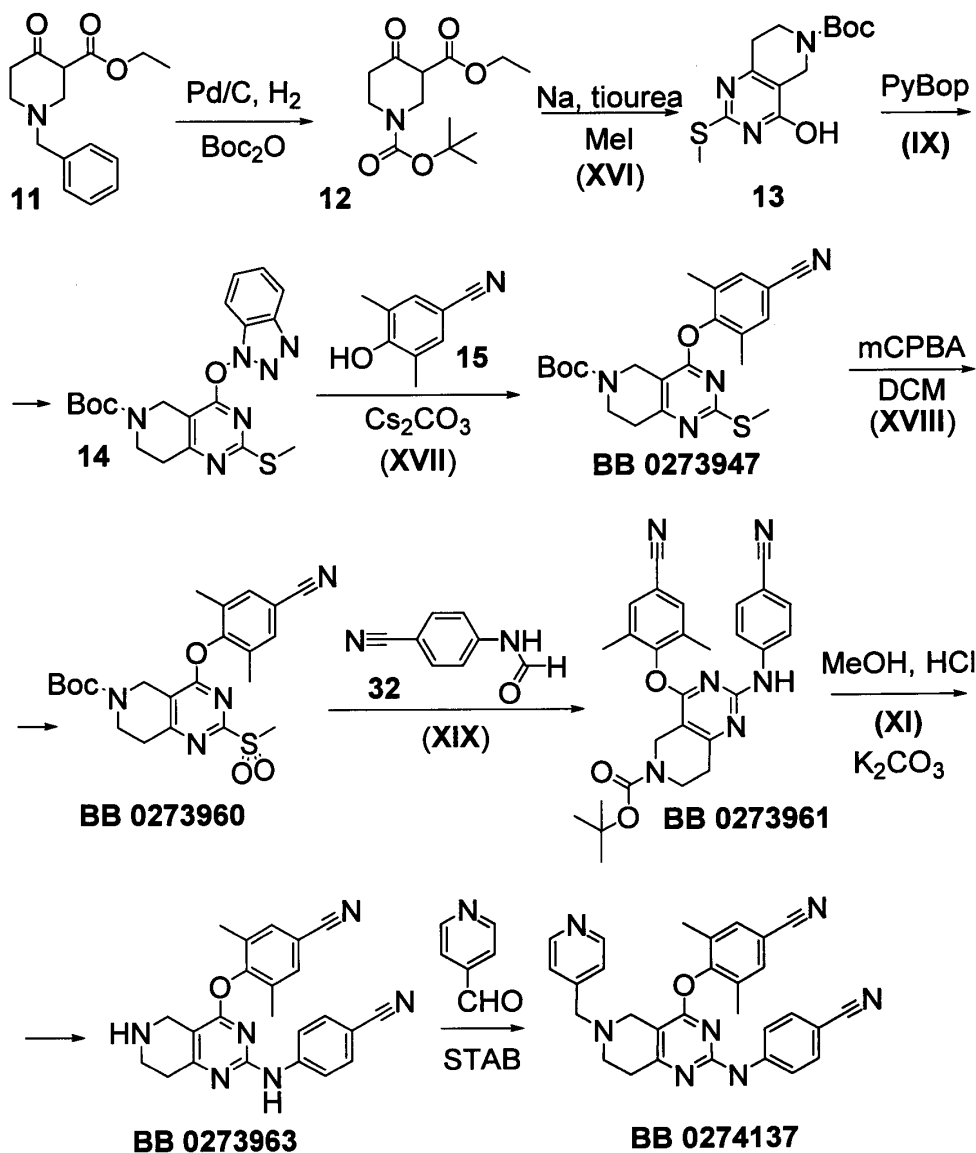
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.10 (broadened singlet, 6H), 2.94 (s, 3H), 3.02-3.20 (m, 4H), 3.40-3.59 (m, 4H), 7.42 (s, 4H), 7.78 (s, 2H), 10.09 (s, 1H).

Weight Yield - 0.08 g (75%)

LCMS m/z (M+H): 489

Example 59.

5 Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(pyridine-4-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274137

¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.12 (s, 6 H), 2.90 (dd, *J*=15.1 Hz, 4.8 Hz,

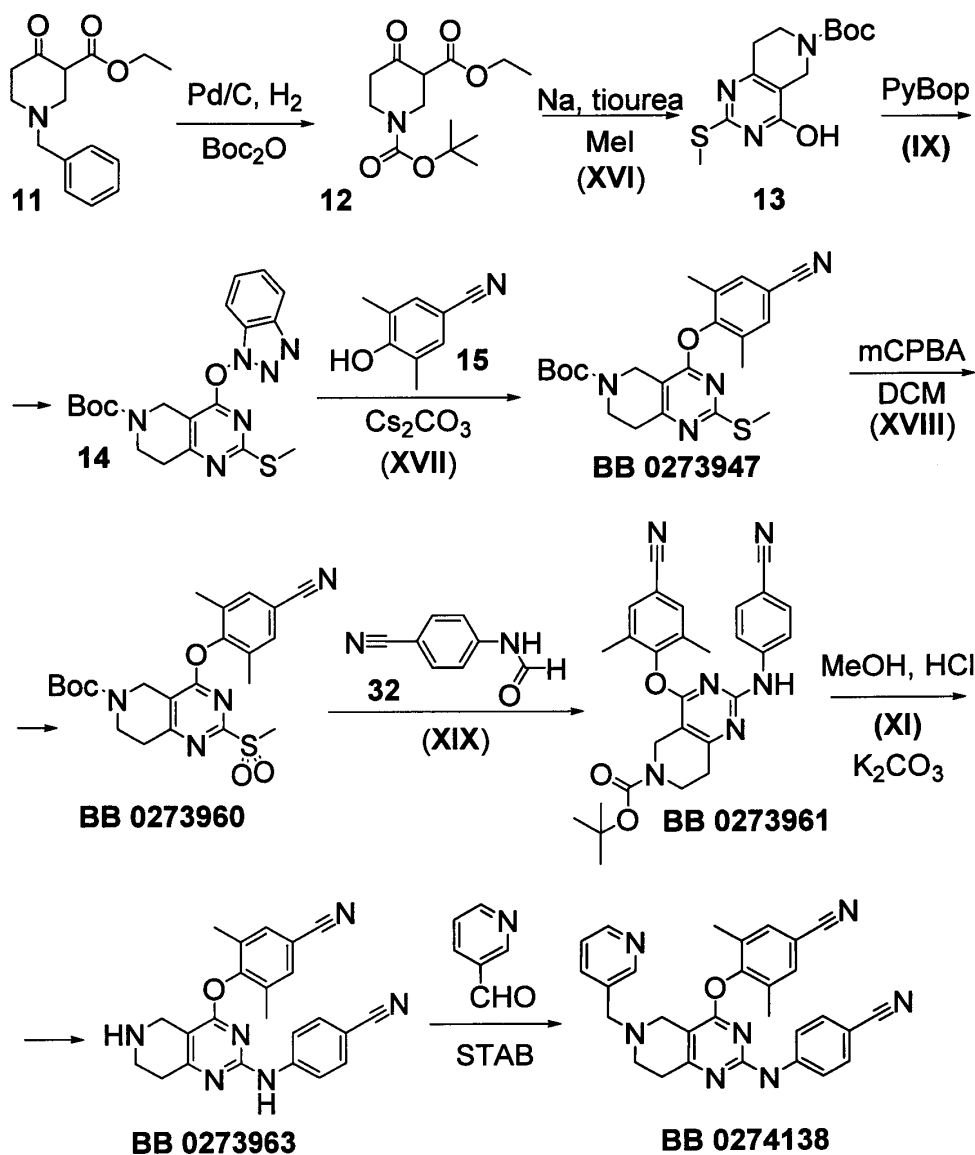
4H), 3.71 (s, 2H), 3.81 (s, 2H), 7.31 - 7.41 (m, 6H), 7.45 (s, 2H), 8.58-8.60 (m, 2H).

Weight Yield - 0.026 g (38%)

LCMS m/z (M+H): 488

Example 60.

Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(pyridine-3-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274138

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.12 (s, 6H), 2.80 - 3.00 (m, 4H), 3.71 (s, 2H),

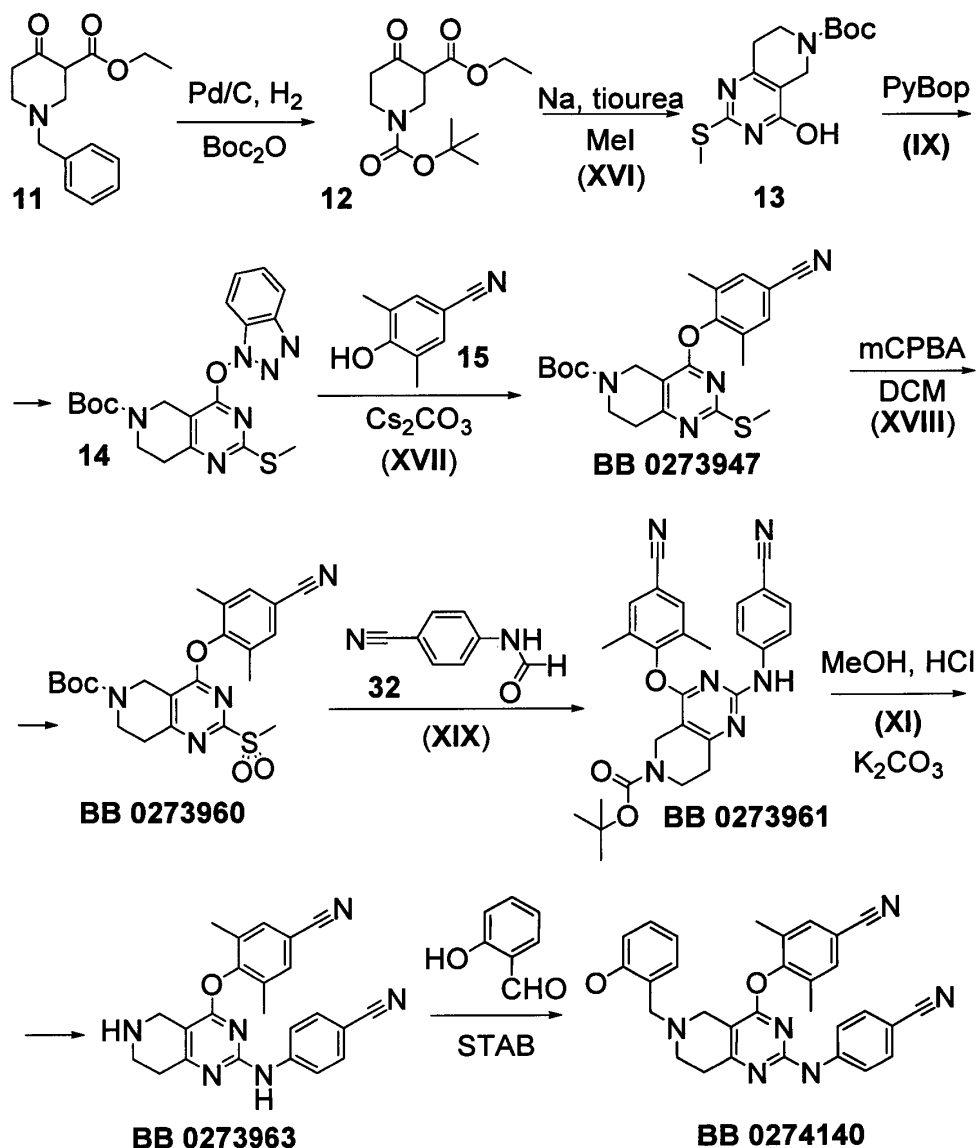
3.81 (s, 2H), 7.28 - 7.41 (m, 4H), 7.46 (s, 2H), 7.50 (dd, $J=7.9$ Hz, 4.8 Hz, 1 H), 7.77 (d, $J=7.8$ Hz, 1H), 8.19 (dt, $J=7.9$ Hz, 1.9 Hz, 1H), 8.53 - 8.68 (m, 1H).

Weight Yield - 0.030 g (40%)

LCMS m/z (M+H): 488

Example 61.

5 Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(2-hydroxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274140

^1H NMR (400 MHz, CDCl_3 , δ , ppm): 2.14 (s, 6H), 3.00 (d, $J=6.6$ Hz, 4 H), 3.83

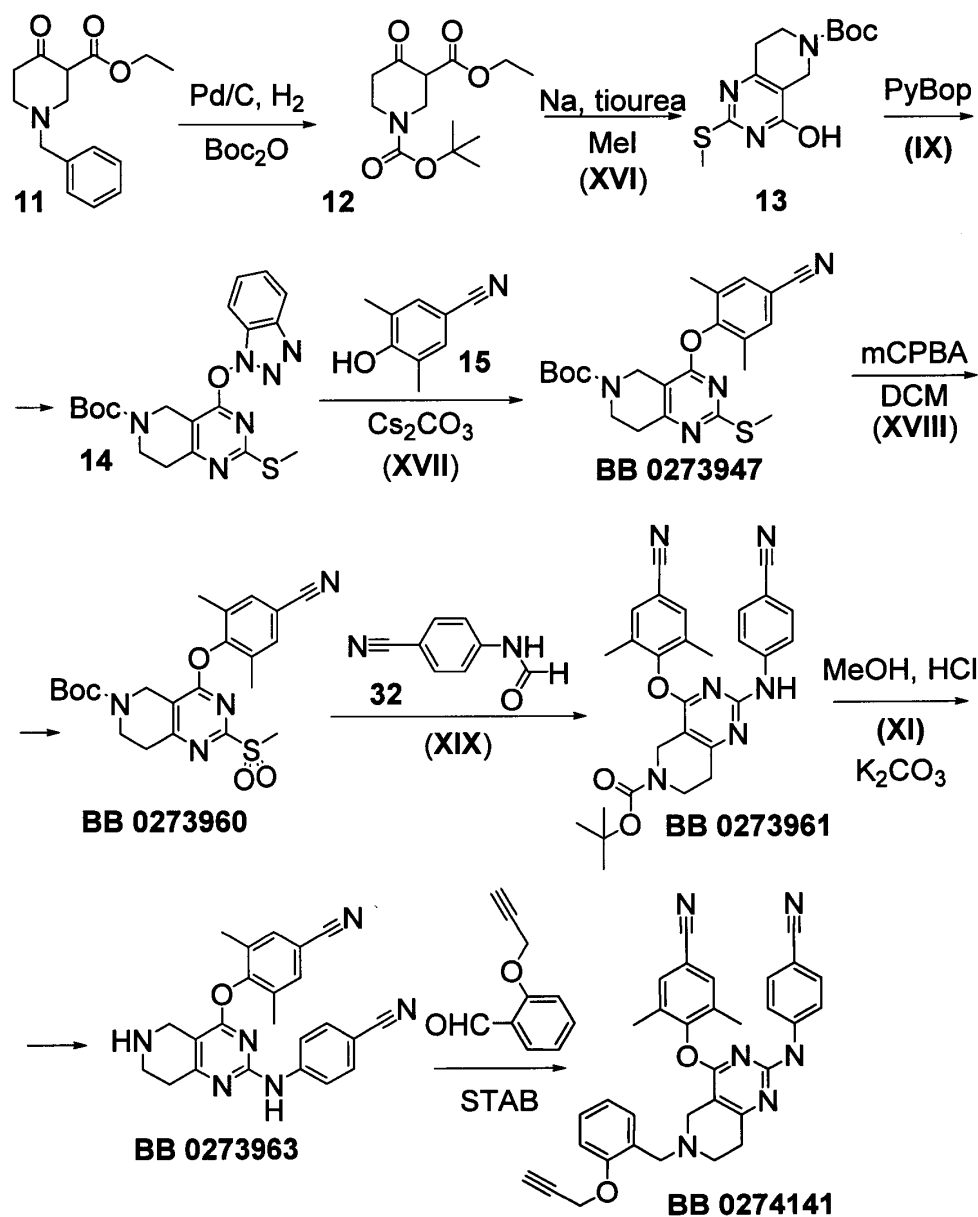
(broadened singlet, 2H), 4.01 (s, 2H), 6.83 - 6.92 (m, 2H), 7.02 - 7.11 (m, 2H), 7.33 - 7.38 (m, 2H), 7.39 - 7.44 (m, 2H), 7.47 (s, 2H).

Weight Yield - 0.033 g (41%)

LCMS m/z (M+H): 503

Example 62.

5 Synthesis of 4-((2-((4-cyanophenyl)amino)-6-(2-(prop-2-yn-1-yloxy)benzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274141

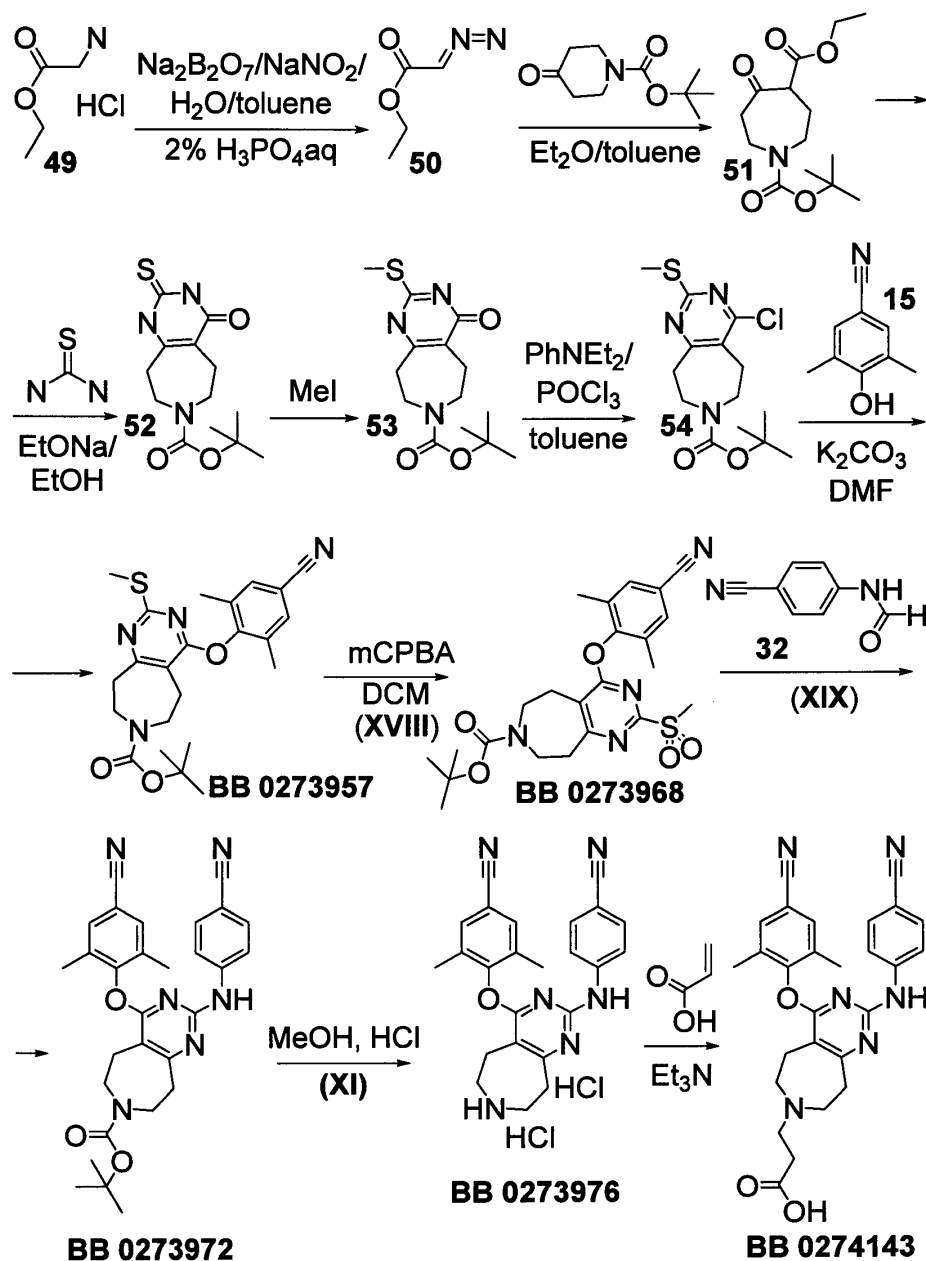
¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.13 (s, 6H), 2.51 (dt, *J*=10.6 Hz, 2.4 Hz, 2H),
2.90 (s, 4H), 3.78 (s, 2H), 3.87 (s, 2H), 4.75 (dd, *J*=8.3 Hz, 2.4 Hz, 2H), 6.95 - 7.07 (m,
5 2H), 7.25 - 7.33 (m, 4H), 7.33 - 7.38 (m, 2H), 7.45 (s, 2H).

Weight Yield - 0.062 g (70%)

LCMS *m/z* (M+H): 541

Example 63.

Synthesis of 3-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)propane acid



5

BB 0274143

^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.01-2.22 (m, 6H), 2.60-2.82 (m, 2H), 3.16 (broadened singlet, 10H), 7.43 (broadened singlet, 4H), 7.79 (s, 2H), 10.09 (broadened

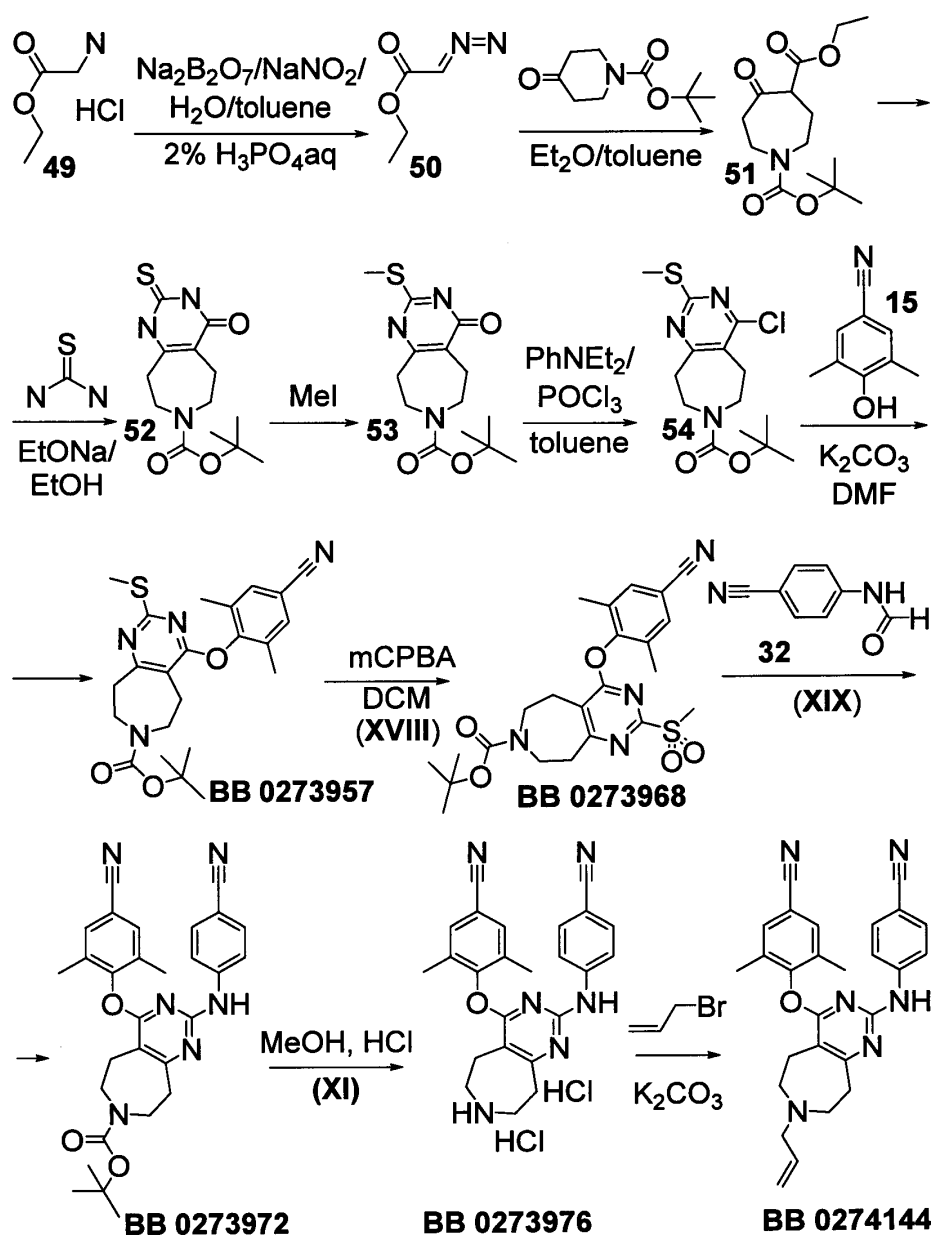
singlet, 1H).

Weight Yield - 0.09 g (33%)

LCMS m/z (M+H): 483

Example 64.

Synthesis of 4-((7-allyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274144

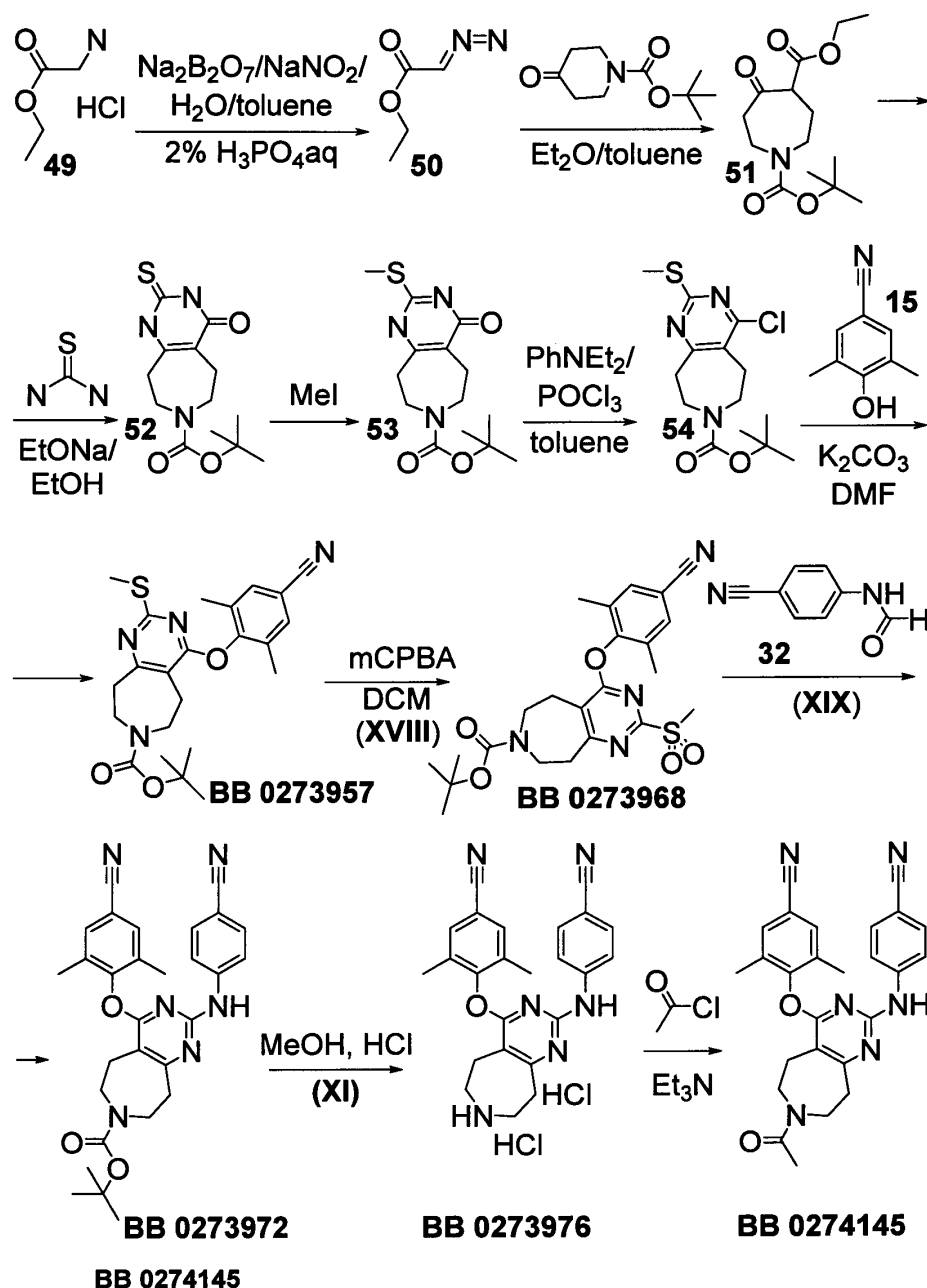
¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.15 (s, 6H), 2.61-2.81 (m, 4H), 3.07 (broadened singlet, 4H), 3.19 (d, *J*=6.2 Hz, 2H), 5.15-5.29 (m, 2H), 5.82-6.03 (m, 1H),
5 7.11 (s, 1H), 7.28-7.33 (m, 2H), 7.34-7.41 (m, 2H), 7.48 (s, 2H).

Weight Yield - 0.011 g (17%)

LCMS *m/z* (M+H): 451

Example 65.

Synthesis of 4-((7-acetyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



BB 0274145

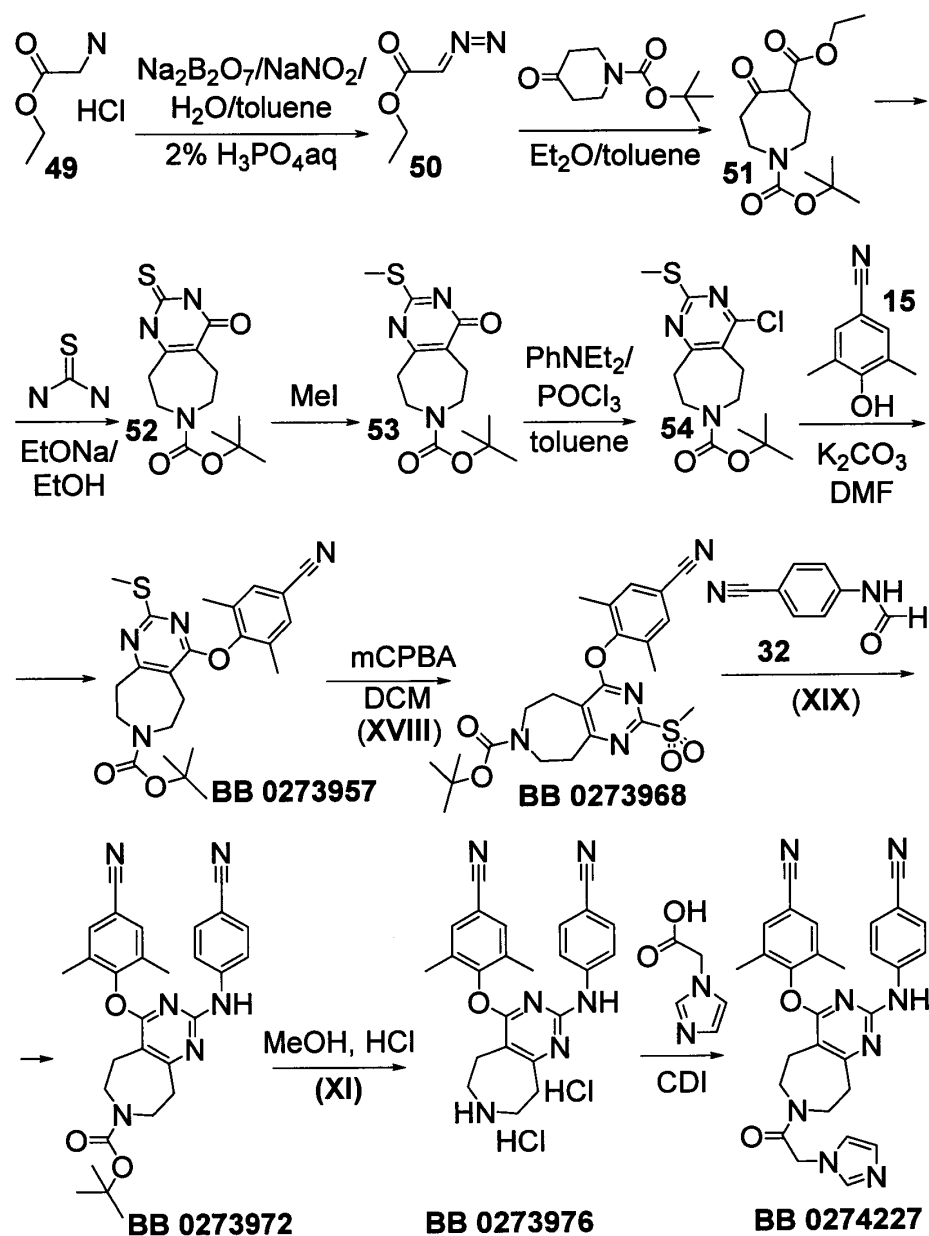
¹H NMR (400 MHz, DMSO-d₆, δ , ppm): 2.10 (broadened singlet, 9H), 2.98 (broadened singlet, 2H), 3.09 (broadened singlet, 2H), 3.70 (broadened singlet, 4H), 7.41 (broadened singlet, 4H), 7.78 (broadened singlet, 2H), 10.06 (broadened singlet, 1H).

Weight Yield - 0.074 g (69%)

LCMS m/z (M+H): 453

Example 66.

Synthesis of 4-((7-(2-(1H-imidazole-1-yl)acetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



165

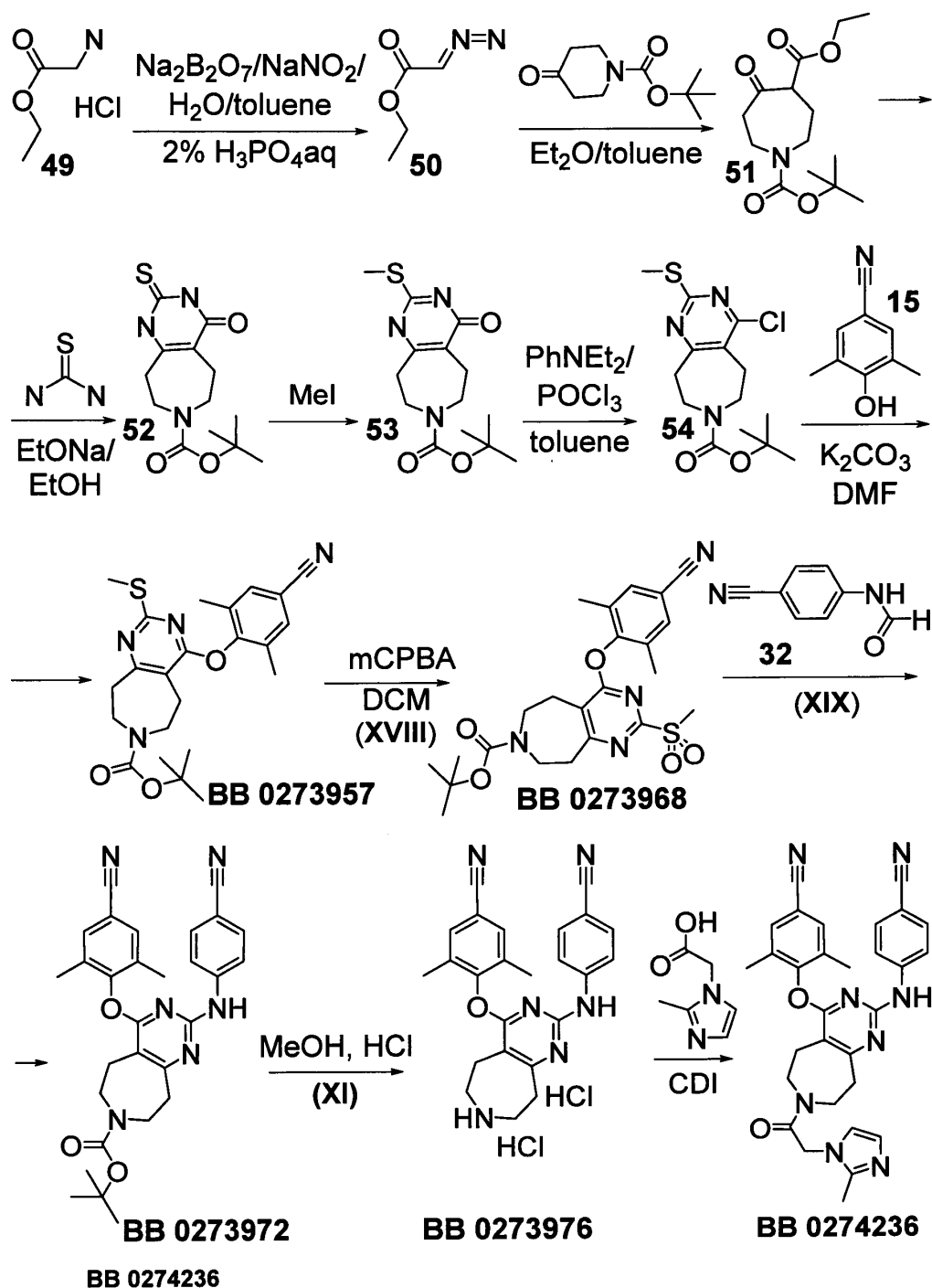
¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.11 (d, *J*=10.2 Hz, 6H), 3.03 (broadened singlet, 2H), 3.17 (broadened singlet, 2H), 3.76 (broadened singlet, 4H), 5.13 (d, *J*=6.1 Hz, 2H), 6.90 (broadened singlet, 1H), 7.10 (d, *J*=7.40 Hz, 1H), 7.43 (d, *J*=5.8 Hz, 4H), 7.61 (d, *J*=6.7 Hz, 1H), 7.79 (d, *J*=6.7 Hz, 2H), 10.08 (broadened singlet, 1H).

5 Weight Yield - 0.011 g (21%)

LCMS *m/z* (M+H): 519

Example 67.

Synthesis of 4-((2-((4-cyanophenyl)amino)-7-(2-(methyl-1H-imidazole-1-yl)acetyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile



167

¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.00-2.23 (m, 9H), 2.92-3.25 (m, 4H), 3.77 (broadened singlet, 4H), 5.02 (d, *J*=13.0 Hz, 2H), 6.69 (d, *J*=5.2 Hz, 1H), 6.96 (d, *J*=11.4 Hz, 1H), 7.43 (d, *J*=6.8 Hz, 4H), 7.79 (d, *J*=7.5 Hz, 2H), 10.08 (broadened singlet, 1H).

M = 0.038 g (41%)

5 LCMS m/z (M+H): 533

10

15

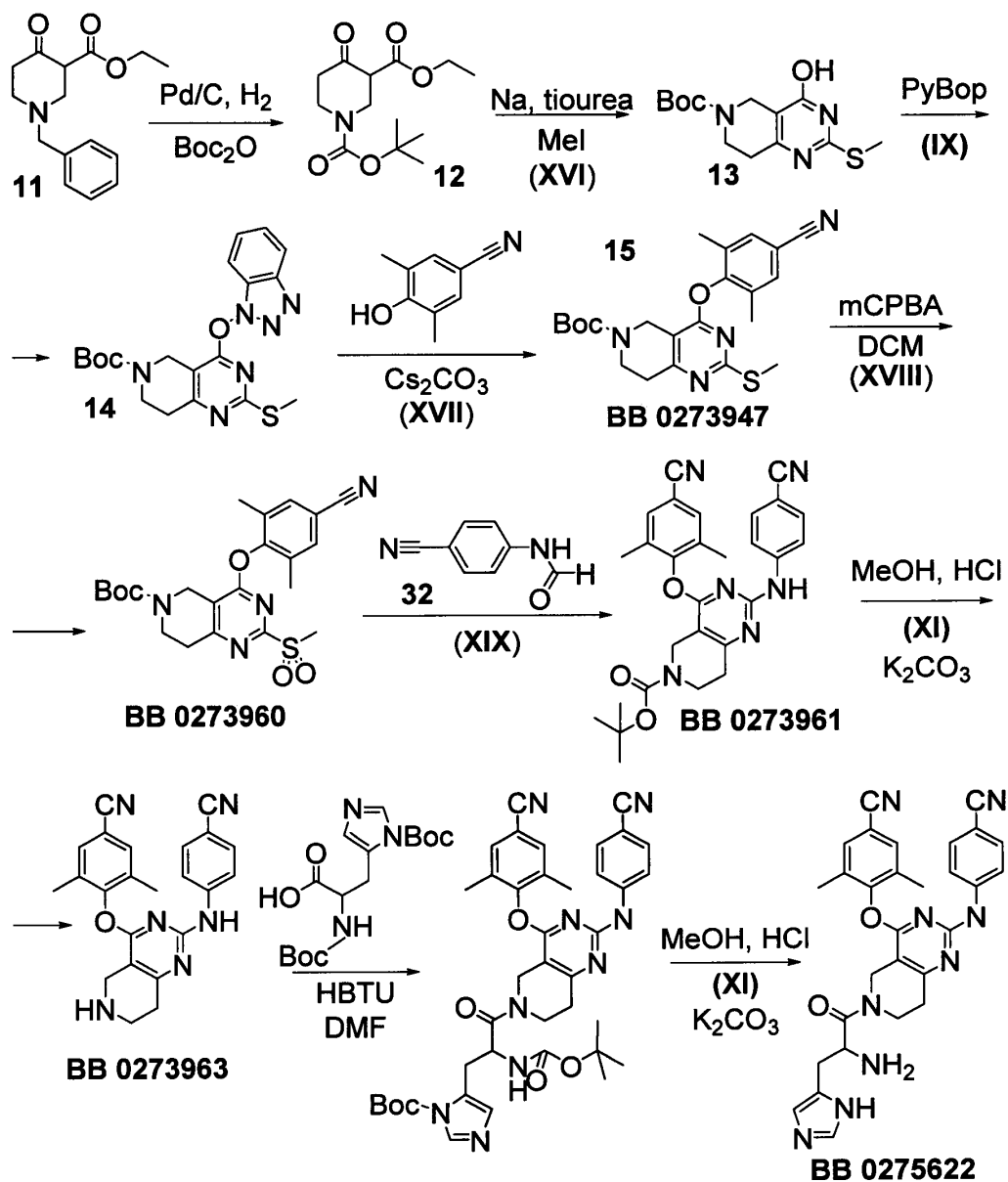
20

25

30

Example 68.

Synthesis of 4-((6-(2-amino-3-(1H-imidazole-5-yl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile



5

BB 0275622

¹H NMR (400 MHz, CDCl₃, δ, ppm): 2.42 (s, 5 H), 2.51 - 2.68 (m, 1 H), 2.73 - 2.92 (m, 1 H), 3.01 - 3.30 (m, 2 H), 3.74 - 3.96 (m, 2 H), 4.05 - 4.33 (m, 1 H), 4.61 - 4.77 (m, 1 H), 4.82 - 4.97 (m, 1 H), 6.94 (d, J=0.9 Hz, 1 H), 7.37 (s, 2 H), 7.47 (dd, J=4.9, 1.0 Hz, 1

H), 7.63 (d, $J=8.7$ Hz, 2 H), 7.83 (d, 2 H)

M = 0.006 g (33%)

LCMS m/z (M+H): 535

5 Evaluation of HIV reproduction inhibition /protection of human cells by anti-HIV products of the present invention was conducted by measuring change in living cells concentration in experimental wells with MT-4 cells infected with HIV-1, as well as by the production of viral protein p24 with adding different concentrations of compounds according to the present invention.

10 Antiviral activity of products against HIV-1 subtype A strain 12RU 69831 was determined, when the cell culture was infected with a constant dose of virus, corresponding to 300 CCID50.

Results of IC50 determination of compounds according to the present invention are provided in table 1.

15 Table 1. Activity of compounds according to the present invention against human immunodeficiency virus HIV-1 subtype A

Compound	Activity against HIV-1 12RU 69831 strain (subtype A), μ M	Compound	Activity against HIV-1 12RU 69831 strain (subtype A), μ M
BB0273459	74.3452	BB0274138	0.00676
BB0274100	33.7972	BB0274140	27.8330
BB0274101	8.80281	BB0274141	173.752
BB0274102	0.00341	BB0274143	0.71014
BB0274103	228.260	BB0274144	1.62971
BB0274111	533.088	BB0274145	1.68874
BB0274118	0.32442	BB0274227	0.01252
BB0274119	102.739	BB0274236	0.04878
BB0274120	108.280	BB0273774	223.844
BB0274121	18.7265	BB0273775	295.399
BB0274122	18.9274	BB0273892	1,223.77
BB0274123	2.06611	BB0273943	346.303
BB0274124	342.424	BB0273961	42.2535
BB0274125	82.1428	BB0273963	7.55667
BB0274126	45.3020	BB0273964	0.14526
BB0274127	12.0967	BB0273965	1.73077
BB0274128	113.114	BB0273969	10683.7

BB0274129	1.03921	BB0273972	117.416
BB0274130	240.000	BB0273976	0.00583
BB0274131	0.66666	BB0274009	290.502
BB0274132	0.90909	BB0274010	0.06201
BB0274133	10.4722	BB0274011	27.1318
BB0274134	0.09594	BB0274012	5.81395
BB0274135	6.13496	BB0274014	5.97609
BB0274137	0.00799	BB0274065	41.118
BB0274015	29.8805	BB0274072	4.065
BB0274016	4880.48	BB0274073	57.425
BB0274021	0.01022	BB0274074	83.333
BB0274025	3215.43	BB0274075	5.802
BB0274026	0.36398	BB0274080	0.414
BB0274027	37.037	BB0274095	11.333
BB0274028	16.194	BB0274097	663.967
BB0274051	0.00552	BB0274098	0.046
BB0274052	0.12745	BB0274099	0.152
BB0274063	230.263	BB0275622	0.032
BB0274064	493.421	BB0274239	359.0485
		BB0274312	34.823
		BB0274337	204.938

Features mentioned in the specification or in the claims expressed in special forms and terms for the implementation of the claimed function or method or way of achievement of the claimed result may be used separately or in any combination of such features to implement the invention in its different forms.

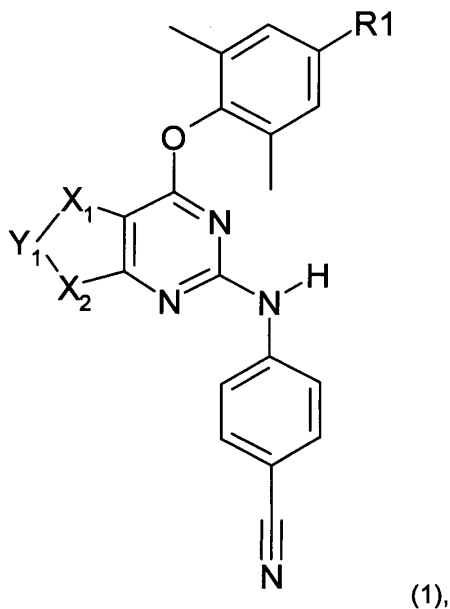
The present invention is described with a reference to illustrations and examples with a purpose of clarification and understanding of the invention essence. It is obvious for the person skilled in the art that within the scope and claims of the invention, different changes and modifications are possible. Consequently, it is assumed that the specification just illustrates the invention and doesn't limit its scope. Scope of the invention is determined with a reference to the claims of the invention including the whole scope of equivalents covered by the claims.

All patents, patent applications and publications cited in the specification are included into the specification as a reference on a full scale in each case at the same extent, as if each patent, patent application and publication were cited separately.

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Claims

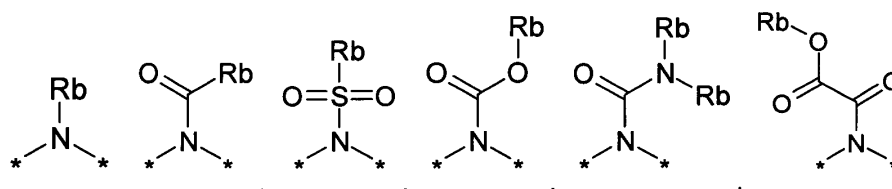
1. Compound of formula I



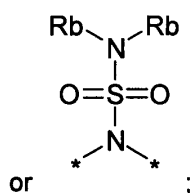
- wherein R^1 is selected independently and represents H, CN, $CN-CH=CH-$, $C=O$,
 5 $CH=CH-COOH$, substituted or unsubstituted 4-6-membered heterocyclyl, containing 1-2
 heteroatom O; aminocarbonyl; NH_2 ; substituted or unsubstituted $C_{1-6}alkyl$; halogen;
 substituted or unsubstituted $C_{1-6}alkyloxy$; NHR^9 ; NR^9R^{10} ; $-C(=O)-NHR^9$; $-C(=O)-NR^9R^{10}$;
 $-C(=O)-R^9$; $-CH=N-NH-C(=O)-R^9$; substituted or unsubstituted $C_{1-6}alkyloxyC_{1-6}alkyl$,
 substituted or unsubstituted $C_{2-6}alkenyl$; substituted or unsubstituted $C_{2-6}alkynyl$; $-C(=N-$
 10 $O-R^8)-C_{1-4}alkyl$; R^7 and $-Rb-R^7$;

X^1 , X^2 represent substituent of $(CH_2)_n$ type, wherein, n is selected independently
 for X_1 , X_2 ;

Y^1 is selected independently and represents $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, or
 substituents of the following type:



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R^b is selected independently and represents -H, cyano, aminocarbonyl, substituted or unsubstituted $-\text{C}_1-\text{C}_6$ -alkyl, substituted or unsubstituted $-\text{C}_2-\text{C}_6$ -alkenyl, substituted or unsubstituted $-\text{C}_2-\text{C}_6$ -alkynyl, substituted or unsubstituted $-\text{C}_3-\text{C}_6$ -aryl, substituted or unsubstituted 4-6-membered-heteroaryl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O, substituted or unsubstituted $-\text{C}_3-\text{C}_9$ -cycloalkyl, substituted or unsubstituted 4-9-membered heterocyclyl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O, R^7 or R^9 ,

wherein R^b may be attached to the rest moiety through a linker of $(\text{CH}_2)_n$ type,

R^7 represents monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic carbocycle or monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic 4-6 membered heterocycle, containing 1 to 4 heteroatoms, independently selected from a group S, N and O, wherein each of the mentioned above carbocyclic or heterocyclic fragments may be optionally substituted by one, two, three, four or five substituents, each of which is independently selected from halogen, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- and di(C_{1-6} alkyl)amino C_{1-6} alkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl, $-\text{C}(=\text{N}-\text{O}-\text{R}^8)$, R^{7a} , $-\text{Rb}-\text{R}^{7a}$, and $\text{R}^{7a}-\text{C}_{1-4}$ alkyl;

R^{7a} represents monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic carbocycle or monocyclic, bicyclic or tricyclic, saturated, partially saturated or aromatic 4-6 membered heterocycle, containing 1 to 4 heteroatoms, independently selected from a group S, N and O, wherein each of the mentioned above carbocyclic or heterocyclic fragments may be optionally substituted by one, two, three, four or five substituents, each of which is independently selected from halogen, hydroxy, mercapto, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio, cyano, nitro, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, aminocarbonyl and $-\text{CH}(=\text{N}-\text{O}-\text{R}^8)$;

R^8 represents hydrogen, C_{1-4} alkyl, aryl or aryl C_{1-4} alkyl.

Each of R^9 and R^{10} independently represents hydrogen; cyano, aminocarbonyl, hydroxy group; C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; amino; mono- or di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyl)aminocarbonyl; $-\text{CH}(=\text{NR}^{11})$ or R^7 ,

wherein each of the abovementioned C₁₋₆alkyl groups may be optionally independently substituted by one or two substituents, each of which is independently selected from hydroxy, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, cyano, amino, aminocarbonyl, imino, mono- and di(C₁₋₄alkyl)amino, polyhalomethyl, polyhalomethyloxy; 5 polyhalomethylthio, -S(=O)_pR⁸, -NH-S(=O)_pR⁸, -C(=O)R⁸, -NHC(=O)H, -C(=O)NHNH₂, NHC(=O)R⁸, C(=NH)R⁸, R⁷

wherein substituents R¹, R^b each independently is selected from a group, comprising: COO-isobutyl, OH, CN, NH₂, C₁₋₄-alkoxy, C₁₋₄alkyl, 4-6-membered heteroaryl, containing 1 to 4 heteroatoms, independently selected from a group S, N and 10 O, in addition, the abovementioned heteroaryl is unsubstituted or substituted with CN, NH₂, OH, C₁₋₆-alkyl, O or R^c; BOC, COOH, R^c, C₃₋₆-aryl, optionally substituted CN, NH₂, OH, O or OCH₂C≡CH, 4-6-membered heterocyclyl, containing 1-3 heteroatom, selected from N, S and O, O, N, S-C₁₋₆-alkyl, halogen, NR⁹R¹⁰, -C(=O)-NR⁹R¹⁰, -C(=O)-C₁₋₆alkyl.

R^c represents NHCOO-C₁₋₆-alkyl,

15 n may have values from 1 to 3.

2. Compound according to claim 1, where

R¹ is selected independently and represents H, CN, CN-CH=CH, C=O, CH=CH-COOH, 4-6-membered heterocyclyl, containing 1-2 heteroatom O;

R^b is selected independently and represents:

20 -H,

substituted or unsubstituted -C₁-C₆-alkyl,

substituted or unsubstituted -C₁-C₆-alkenyl,

substituted or unsubstituted -C₃-C₆-aryl,

25 substituted or unsubstituted -5-6-membered-heteroaryl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O,

substituted or unsubstituted -C₃-C₉-cycloalkyl, or

substituted or unsubstituted 4-9-membered heterocyclyl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O,

30 wherein the mentioned above substituents R^b, each independently is selected from a group, comprising:

COO-isobutyl,

NH₂,

CN,

C₁₋₄-alkoxy,

4-6-membered heteroaryl, containing 1 to 4 heteroatoms, independently selected from a group S, N and O, in addition, the abovementioned heteroaryl is unsubstituted or substituted with OH, C₁₋₆-alkyl, O or R^c;

BOC;

5 COOH;

R^c ;

C3-6-aryl, optionally substituted OH, O or OCH₂C≡CH,

4-6-membered heterocyclyl, containing 1-2 heteroatom selected from N and O,

10 O, N,

S-C₁₋₆-alkyl,

halogen,

the remaining radicals are as determined in claim 1.

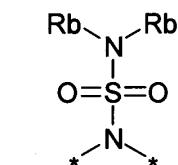
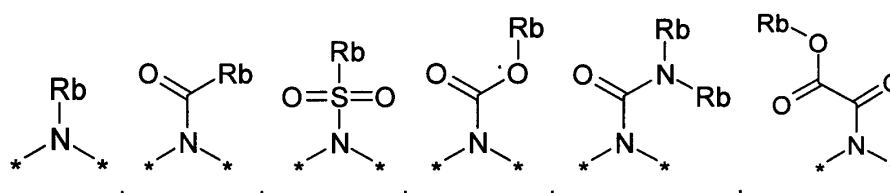
3. Compound according to claim 1, wherein R¹ is selected independently and represents H, -CN, -CH=CH-CN, -C=O or -CH=CH-COOH.

4. Compound according to claim 1, wherein R¹ is selected independently and represents 4-6-membered heterocyclyl, containing 1-2 heteroatom O.

5. Compound according to claim 3, wherein R¹ represents oxetane, tetrahydrofuran or tetrahydropyran.

20 6. Compound according to claim 1, wherein Y¹ represents -O-, -S-, -S(=O)- or -S(=O)₂-.

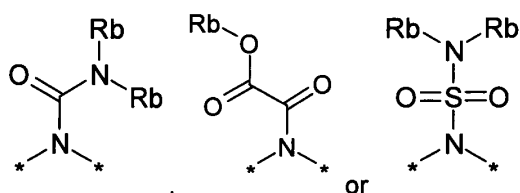
7. Compound according to claim 1, wherein Y¹ is substituents of the following type:



or

25 8. Compound according to claim 1, wherein Y¹ is substituents of the following type:

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9. Compound according to claim 1, wherein R^b is substituted or unsubstituted methyl, ethyl, propyl, n-propyl, isopropyl, butyl, n-butyl, sec-butyl, tert-butyl or pentyl, wherein substituents are such, as determined in claim 1.

5 10. Compound according to claim 1, wherein R^b is substituted or unsubstituted ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl, wherein substituents are as determined in claim 1.

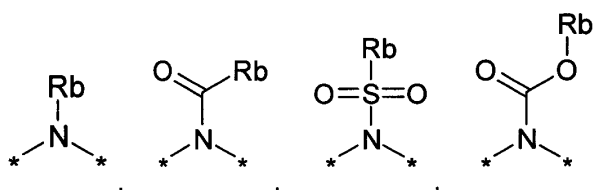
11. Compound according to claim 1, wherein R^b is substituted or unsubstituted phenyl, wherein substituents are as determined in claim 1.

10 12. Compound according to claim 1, wherein R^b is substituted or unsubstituted thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazolyl, benzo[b]thienyl, isobenzofuranyl, isoindolyl, benzimidazolyl, wherein substituents are as determined in claim 1.

15 13. Compound according to claim 1, wherein R^b is substituted or unsubstituted cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.2]octanyl, spiro[5.5]undecanyl, wherein substituents are as determined in claim 1.

14. Compound according to claim 1, wherein R^b is substituted or unsubstituted pyrimidine, piperidine, azetidine, morpholine, piperazine, pyrrolidine, tetrahydropyran, furan, pyrrol, pyrazine, imidazole or pyrazole.

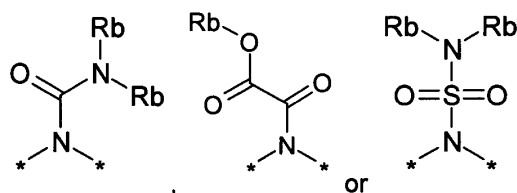
20 15. Compound according to claim 1, wherein Y^1 is substituents of the following type:



25 a R^b is substituted or unsubstituted -5-6-membered-heteroaryl or heterocyclyl, containing 1 to 4 heteroatoms, independently selected from N, S and/or O, wherein substituents are as determined in claim 1.

16. Compound according to claim 1, wherein Y^1 is substituents of the following type:

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–C₃–C₆–aryl or substituted or unsubstituted –C₃–C₉–cycloalkyl, wherein substituents are as determined in claim 1.

17. Compound selected from:

4-((4-(2,6-Dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-yl)amino)-benzonitrile

4-(2,6-Dimethylphenoxy)-N-(piperidine-4-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine

Ethyl ether 4-(((6-benzyl-4-(4-cyano-2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid

Ethyl ether 4-(((6-benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2-yl)amino)methyl)benzoic acid

4-(((7-Benzyl-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2-yl)amino)methyl)benzonitrile

N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-5,6,7,8-tetrahydroquinazoline-2-amine

N-(1-Benzylpiperidine-4-yl)-4-(2,6-dimethylphenoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2-amine

4-((2-((4-Cyanophenyl)amino)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((4-(4-Formyl-2,6-dimethylphenoxy)-7-methyl-5,6,7,8-tetrahydro[3,4-d]pyrimidine-2-yl)amino)benzonitrile

Tert-butyl 4-(4-(1,3-dioxolane-2-yl)-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-formyl-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

Ethyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

(E)-3-(4-((7-(Tert-butoxycarbonyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylphenyl)acrylic acid

Tert-butyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 2-((4-cyanophenyl)amino)-4-(4-(2-cyanovinyl)-2,6-dimethylphenoxy)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-picolynoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-isonicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-nicotinoyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-2-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-3-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(pyridine-4-ylmethyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)piperidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-carbonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-yl)piperidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(piperidine-4-yl)-6,7,8,9-tetrahydro-5H-

pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((6-(2-Aminoacetyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(2-(3-hydroxyazetidine-1-yl)acetyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-({2-[(4-Cyanophenyl)amino]-6-[2-(morpholine-4-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl}oxy)-3,5-dimethylbenzonitrile

4-({2-[(4-Cyanophenyl)amino]-6-[2-(4,4-difluoropiperidine-1-yl)acetyl]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl}oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(cyclopropanecarbonyl)-5,6,7,8-tetrahydro-[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-({2-[(4-Cyanophenyl)amino]-6-(morpholine-4-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl}oxy)-3,5-dimethylbenzonitrile

4-({2-[(4-Cyanophenyl)amino]-6-(4-methylpiperazine-1-carbonyl)-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl}oxy)-3,5-dimethylbenzonitrile

Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate

(R)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate

(S)-Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-7-carbonyl)pyrrolidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(tetrahydro-2H-pyran-4-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(5-methylfuran-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(1-methyl-1H-pyrrol-2-yl)methyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(4-hydroxybenzyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(1-methoxypropane-2-yl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 2-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-6-carbonyl)pyrrolidine-1-carboxylate

4-((2-((4-Cyanophenyl)amino)-6-(pyrrolidine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((6-(Azetidine-3-carbonyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyrazine-2-carbonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxopropane-2-yl)carbamate

(S)-4-((6-(2-Aminopropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-1-oxo-3-phenylpropane-2-yl)carbamate

(S)-4-((6-(2-Amino-3-phenylpropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-7-(2-morpholineoEthyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-hydroxy-1-oxopropane-2-yl)carbamate

Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-(methylthio)-1-oxobutane-2-yl)carbamate

4-((6-[2-Amino-3-(1H-imidazole-5-yl)propanoyl]-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((6-(2-Amino-3-(1H-pyrazole-4-yl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

Tert-butyl 4-(2-((tert-butoxycarbonyl)amino)-3-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-oxopropyl)-1H-pyrazole-1-carboxylate

(R)-4-((6-(2-Amino-3-hydroxypropanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-

cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-(4-hydroxyphenyl)-1-oxopropane-2-yl)carbamate

(S)-4-((6-(2-Amino-3-(4-hydroxyphenyl)propanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(R)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-3-methyl-1-oxobutane-2-yl)carbamate

(R)-4-((6-(2-Amino-3-methylbutanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-Tert-butyl (1-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-4-methyl-1-oxopentane-2-yl)carbamate

(S)-4-((6-(2-Amino-4-methylpentanoyl)-2-((4-cyanophenyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

(S)-di-Tert-butyl (6-(4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-yl)-6-oxohexane-1,5-diyl)dicarbamate

(S)-4-((2-((4-Cyanophenyl)amino)-6-(2,6-diaminohexanoyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-(2-Chloroacetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

Methyl 4-(4-cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-5H-pyrimido[4,5-d]azepine-7(6H)-carboxylate

4-((2-((4-Cyanophenyl)amino)-7-(methylsulfonyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyridine-4-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(pyridine-3-ylmethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(2-hydroxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((2-((4-Cyanophenyl)amino)-6-(2-(prop-2-in-1-yloxy)benzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-4-yl)oxy)-3,5-dimethylbenzonitrile

3-(4-(4-Cyano-2,6-dimethylphenoxy)-2-((4-cyanophenyl)amino)-8,9-dihydro-

5H- pyrimido[4,5-d]azepine-7(6H)-yl)propanoic acid

4-((7-Allyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H- pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-Acetyl-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-(2-(1H-Imidazole-1-yl)acetyl)-2-((4-cyanophenyl)amino)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-((7-((4-Cyanophenyl)amino)-7-(2-(methyl-1H-imidazole-1-yl)acetyl)-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine-4-yl)oxy)-3,5-dimethylbenzonitrile

4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-6-sulfonamide

Methyl 2-{2-[(4-cyanophenyl)amino]-4-(4-formyl-2,6-dimethylphenoxy)-5H,6H,7H,8H,9H-pyrimido [4,5-d]azepine-7-yl}-2-oxoacetate

4-(4-Cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]-N-(oxane-4-yl)-4aH,5H,6H,7H,8H,8aH-pyrido [4,3-d]pyrimidine-6-carboxamide.

18. Compound according to any of claims 1-17, which comprises at least one isotope.

19. Compound according to any of claims 1-17 in the form of a free base

or pharmaceutically acceptable salts selected from a group, comprising salts of amino groups formed by inorganic acids, such as hydrochloric, hydrobromic, phosphoric, sulfuric and chloric acids, or formed by organic acids, such as acetic, oxalic, maleic, tartaric, succinic or malonic acids,

or pharmaceutically acceptable salts: adipate, alginate, ascorbate, aspartate, benzene sulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphor sulfonate, citrate, cyclopentanepropionate, digluconate, dodecyl sulfate, ethane sulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethane sulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalene sulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate,

or pharmaceutically acceptable salts, containing alkaline and/or alkaline-earth metals or nontoxic cations of ammonium, quaternary ammonium and amine,

or pharmaceutically acceptable salts, obtained using counterions, such as

halogenides, hydroxides, carboxylates, sulfates, phosphates, nitrates, lower alkyl sulfonates and aryl sulfonates.

20. Compound according to any of claims 1-17 for the use as an inhibitor of HIV reverse transcriptase.

5 **21.** Compound according to any of claims 1-17 for the use as a pharmaceutical preparation, having anti-HIV antiviral activity.

22. Compound according to any of claims 1-17 for obtaining of a pharmaceutical preparation, having anti-HIV antiviral activity.

10 **23.** Pharmaceutical composition, having activity against reverse transcriptase, comprising the compound according to any of claims 1-17 in a therapeutically effective amount and at least one carrier, excipient or diluent.

24. Pharmaceutical composition for the treatment or prevention of HIV, comprising at least one compound according to any of claims 1-17 in a therapeutically effective amount and at least one carrier, excipient or diluent.

15 **25.** A pharmaceutical composition, having activity against HIV reverse transcriptase, comprising the compound according to any of claims 1-17 in a therapeutically effective amount, and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry
20 inhibitors.

26. A pharmaceutical composition, having activity against HIV reverse transcriptase, wherein HIV reverse transcriptase contains at least one mutation compared to Wild type HIV, comprising the compound according to any of claims 1-17 in a therapeutically effective amount.

25 **27.** A pharmaceutical composition, having activity against HIV reverse transcriptase, wherein HIV reverse transcriptase has reduced sensitivity to Efavirenz, Nevirapine, Doravirine or Delavirdine, comprising the compound according to any of claims 1-17 in a therapeutically effective amount.

28. A pharmaceutical composition for obtaining of an agent for the treatment or
30 prevention of HIV, comprising at least one compound according to any of claims 1-17 in a therapeutically effective amount and pharmaceutically acceptable carrier.

29. Use of compounds according to any of claims 1-17 for obtaining of an agent for the treatment or prevention of HIV.

35 **30.** Use of the composition according to claim 23 for obtaining of an agent for the treatment or prevention of HIV.

31. Method for the treatment or prevention of HIV, including the use of compounds according to any of claims 1-17.

32. Method for the treatment or prevention of HIV, including the use of composition according to any of claims 23-28.

5 **33.** Method for the treatment or prevention of HIV infection, consisting of a subject as needed for treatment being administered with a therapeutically effective amount of compounds according to any of claims 1-17.

10 **34.** Method according to claim 33, wherein the specified therapeutically effective amount of compounds means a daily dose, which is approximately 0.1 - approximately 500 mg/kg body weight in parenteral infusion.

35. Method according to claim 31 and 32, wherein daily dose may be administered as a single dose or in 1-5 divided doses.

15 **36.** Combination for the treatment or prevention of HIV-mediated diseases, including therapeutically effective amount of compounds according to any of claims 1-17 and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors.

20 **37.** Method for the treatment or prevention of HIV-mediated diseases, consisting of a subject as needed for treatment being administered with therapeutically effective amount of compounds according to any of claims 1-17 and at least one compound selected from a group, comprising HIV protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 antagonists and viral cell entry inhibitors.

25 **38.** Method of inhibition of HIV reverse transcriptase in the body of a HIV infected subject, consisting of a subject as needed for treatment being administered with a therapeutically effective amount of compounds according to any of claims 1-17.

39. Method of obtaining of a pharmaceutical composition according to claim 23, consisting of mixing compounds according to claims 1-17 with pharmaceutically acceptable carriers.

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