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(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; 340 Kingsland Street, Nutley, New Jersey 07110 (US).

(72) Inventors: **WANG, Jianhua**; Room 502, Building 6, No. 898, Jia Lin Road, Jin Qiao Town, Pudong New District Shanghai, 201206 (CN). **WANG, Min**; Room 301, Building 23, No. 666, Gaoxing Road, Xinzhuang Town, Min Hang District, Shanghai, 201100 (CN). **YANG, Song**; Room 502, Building 67, No. 1155, Guanglan Road, Zhangjian, Pudong, Shanghai, 201210 (CN). **ZHOU, Chengang**; Room 701, Unit 5, No. 218, Miaopu Road, Pudong District, Shanghai, 200135 (CN).

(74) Agent: **ZHUANG PLODECK, Jianping**; Grenzacherstrasse 124, CH-4070 Basel (CH).

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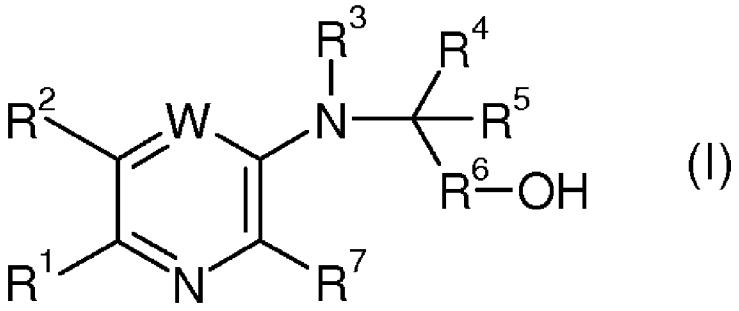
(54) Title: NOVE PHENYL/PYRIDINE SERIES SUBSTITUED BY HYDROXYETHYLAMINO FOR THE TREATMENT OF CANCER



(I)

(57) Abstract: The invention provides novel compounds having the general formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and W are as described herein, compositions including the compounds and methods of using the compounds.

NOVE PHENYL/PYRIDINE SERIES SUBSTITUED BY HYDROXYETHYLAMINO FOR THE TREATMENT OF CANCER

The present invention relates to organic compounds useful for therapy in a mammal, and in particular to inhibit cell proliferation and induce cell cycle arrest and apoptosis that overexpress CDK8 or Cyclin C useful for treating cancer.

FIELD OF THE INVENTION

The cyclin-dependent kinase (CDK) complexes are well-conserved Ser/Thr kinase family, and it has been shown to be activated by the binding of regulatory partner, generally a cyclin. There are total 20 CDK family members and 5 CDK-like proteins based on the similarities in sequence and function. CDKs regulate various key transitions of cell cycle and play an important role in the regulation of transcription, apoptosis and neuronal functions.

Dysregulation of CDKs has been linked to pathological events and both proliferative and non-proliferative disease, including cancers, Alzhemers disease (AD), parkinson's disease, Stroke/ischemia, pain, traumatic brain injury, kidney disease, inflammation pathologies, type 2 diabetes, viral infection (HSV, HCMV, HPV, HIV).

CDK8 is a CyclinC-dependent CDK family kinase and functions as a transcriptional regulator. Several phosphorylation targets of CDK8 have been identified, including the RNA polymerase II (RNAPII) C-terminal domain (CTD), histone H3, subunits of general transcription factors (GTFs) and certain transactivators. CDK8 has also been described as a transcriptional coactivator in oncongenic signaling pathways, including the β-catenin pathway, the serum response network, the Tumor Growth Factor TGFβ signaling pathway, the p53 pathway, as well as in thyroid hormone-dependent transcription. Colocalization of CDK8 and Cyclin C was also reported in neurodegenerative disease such as AD. CDK8 was found to be frequently dysregulated in various human cancers, such as colon cancer, gastric cancer and melanoma. Inhibition of CDK8 by short hairpin RNA (shRNA) inhibits cancer cell proliferation, and induces cell cycle arrest and apoptosis *in vitro* and *in vivo* models. Although Silibinin, the major active constituent of silymarin isolated from milk thistle (Silybum marianum), has shown strong

cell growth inhibition in colon cancer through downregulation CDK8 expression, there are no known direct CDK8 inhibitors under clinical development. Therefore, there is a great unmet medical need to develop CDK8 inhibitors for cancer patients.

SUMMARY OF THE INVENTION

Objects of the present invention are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I for the treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term "C_{1-6}alkyl" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, 1-butyl, 2-butyl, *tert*-butyl and the like. Particular "C_{1-6}alkyl" groups are methyl, ethyl, isopropyl and *tert*-butyl.

The term "C_{1-6}alkoxy" alone or in combination signifies a group C_{1-6}alkyl-O-, wherein the "C_{1-6}alkyl" is as defined above; for example methoxy, ethoxy, propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, 2-butoxy, *tert*-butoxy and the like. Particular "C_{1-6}alkoxy" groups are methoxy and ethoxy and more particularly methoxy.

The term "C_xH_{2x}" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

The term "C_yH_{2y}" alone or in combination signifies a saturated, linear- or branched chain alkyl group containing 2 to 6, particularly 2 to 4 carbon atoms.

The term "cycloalkyl", alone or in combination, refers to a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular "cycloalkyl" groups are cyclopropyl, cyclopentyl and cyclohexyl.

The term "amino", alone or in combination, refers to primary ($-NH_2$), secondary (-NH-) or tertiary amino ().

The term "halogen" means fluorine, chlorine, bromine or iodine. Halogen is particularly fluorine or chlorine.

The term "hydroxy" alone or in combination refers to the group -OH.

The term "carbonyl" alone or in combination refers to the group -C(O)-.

The term "carboxy" alone or in combination refers to the group -COOH.

The term "cyano" alone or in combination refers to the group -CN.

The term "halophenyl" means phenyl substituted by halogen.

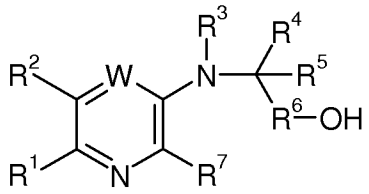
The term "sulfonyl" alone or in combination refers to the group -$S(O)_2$-.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., *et al.*, Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., *et al.*, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457. Particular are the sodium salts of the compounds of formula I.

Compounds of the general formula I which contain one or several chiral centers can either be present as racemates, diastereomeric mixtures, or optically active single isomers. The racemates can be separated according to known methods into the enantiomers. Particularly, diastereomeric salts which can be separated by crystallization are formed from the racemic mixtures by reaction with an optically active acid such as e.g. D- or L-tartaric acid, mandelic acid, malic acid, lactic acid or camphorsulfonic acid.

INHIBITORS OF CDK8 OR CYCLIN C

The present invention provides (i) novel compounds having the general formula I:



(I)

wherein

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is phenyl, pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice or three times substituted by amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylsulfonyl, carboxy, cyano, halogen, hydroxy, hydroxy-C_xH_{2x}-, hydroxy-C_yH_{2y}-aminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl, cycloalkyl, phenyl, halophenyl, phenyl-C_xH_{2x}- or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cycloalkyl;

R^6 is -C_xH_{2x}- or cycloalkyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cycloalkyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

x is 1-6;

y is 2-6;

or pharmaceutically acceptable salt thereof.

Further embodiment of present invention is (ii) a compound of formula I, wherein

R^1 is hydrogen or methyl;

R^2 is phenyl, pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice or three times substituted by amino, aminocarbonyl, methoxy, methyl, ethyl, methylaminocarbonyl, methylsulfonyl, carboxy, cyano, fluoro, chloro, hydroxy, hydroxymethyl, hydroxyethylaminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclohexyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, phenylmethyl or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cyclopentyl;

R^6 is $-CH_2-$, $-C(CH_3)_2$ or cyclohexyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cyclohexyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

or pharmaceutically acceptable salt thereof.

Another embodiment of present invention is (iii) a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen;

R^2 is pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice substituted by amino, C_{1-6}alkoxy, halogen or hydroxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is C_{1-6}alkyl or phenyl;

R^6 is $-C_xH_{2x}-$;

R^7 is hydrogen;

W is -N- or -CH;

x is 1-6.

Further embodiment of present invention is (iv) a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen;

R^2 is pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice substituted by amino, methoxy, fluoro, chloro or hydroxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is ethyl or phenyl;

R^6 is $-CH_2-$;

R^7 is hydrogen;

W is -N- or -CH.

Another embodiment of present invention is (v) a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is phenyl; which is once or twice or three times substituted by amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylsulfonyl, carboxy, cyano, halogen, hydroxy, hydroxy-C_xH_{2x}-, hydroxy-C_yH_{2y}-aminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl, cycloalkyl, phenyl, halophenyl, phenyl-C_xH_{2x}- or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cycloalkyl;

R^6 is -C_xH_{2x}- or cycloalkyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cycloalkyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

x is 1-6;

y is 2-6.

Further embodiment of present invention is (vi) a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen or methyl;

R^2 is phenyl; which is once or twice or three times substituted by amino, aminocarbonyl, methoxy, methyl, ethyl, methylaminocarbonyl, methylsulfonyl, carboxy, cyano, fluoro, chloro, hydroxy, hydroxymethyl, hydroxyethylaminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclohexyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, phenylmethyl or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cyclopentyl;

R^6 is -CH_2-, -$C(CH_3)_2$ or cyclohexyl;

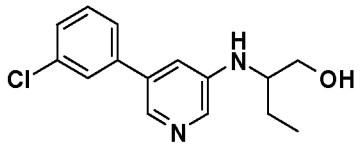
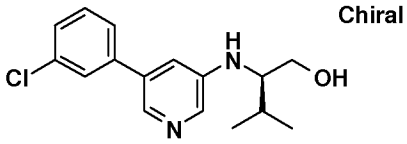
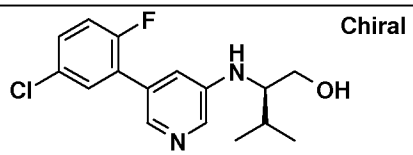
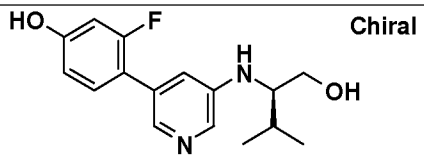
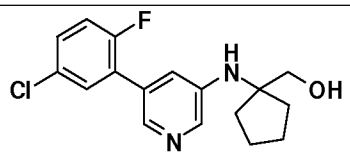
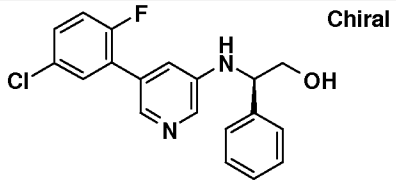
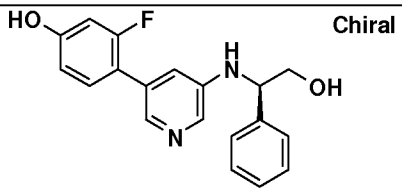
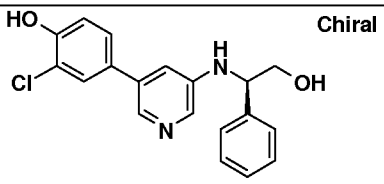
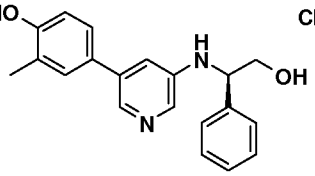
or R^5 and R^6, together with the carbon atom, to which they are attached, form cyclohexyl;

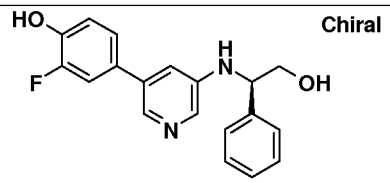
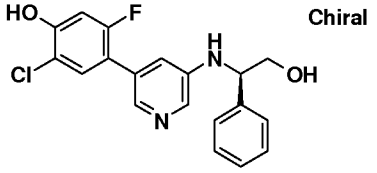
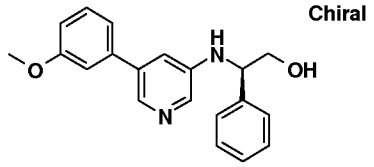
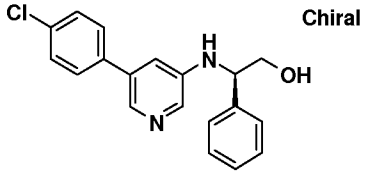
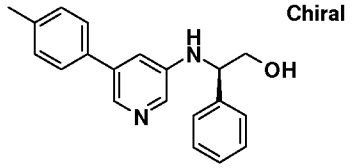
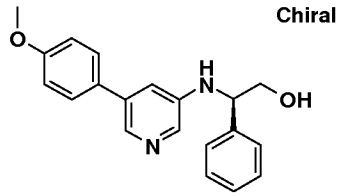
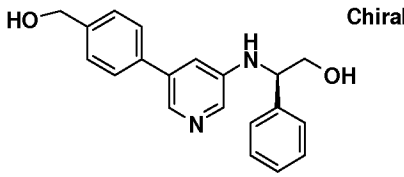
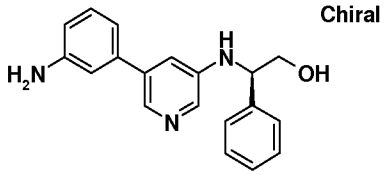
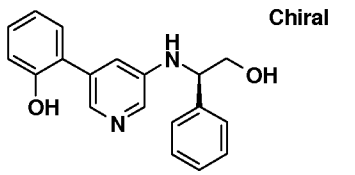
R^7 is hydrogen or amino;

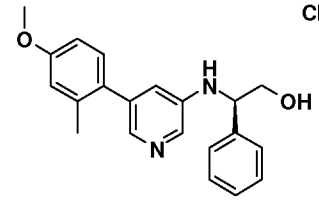
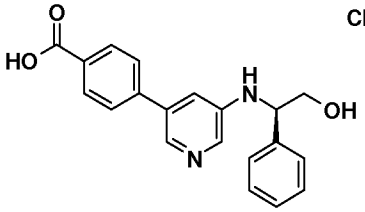
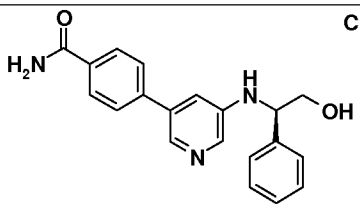
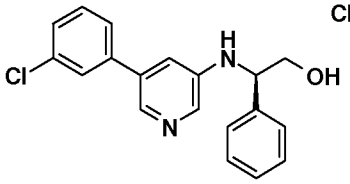
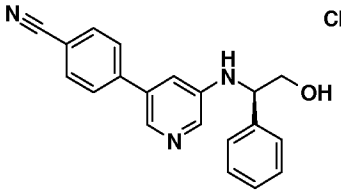
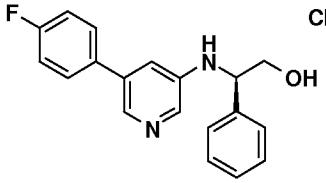
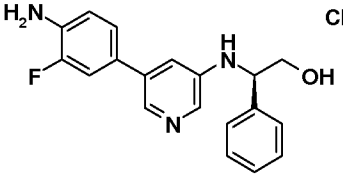
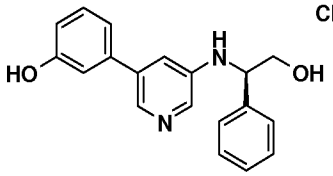
W is -N- or -CH.

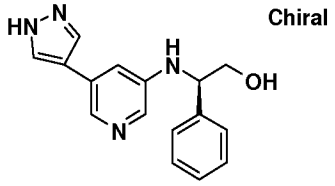
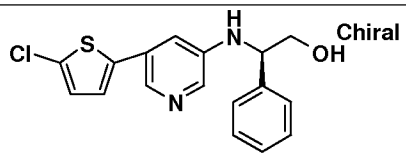
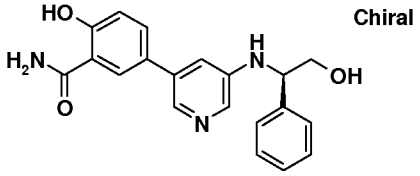
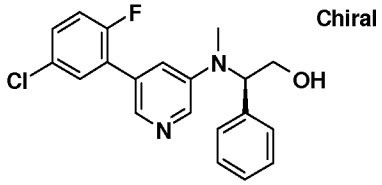
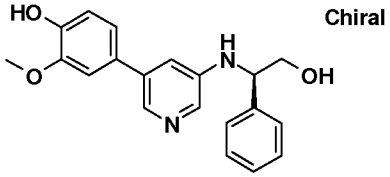
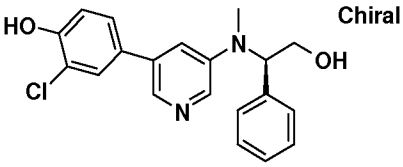
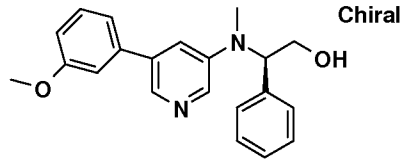
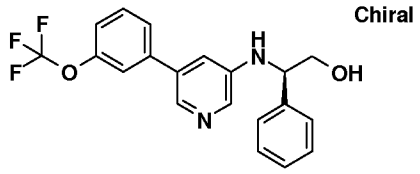
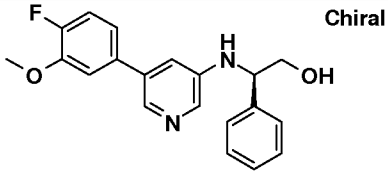
Particular compounds of formula I, including their activity data, NMR data and MS data are summarized in the following Table 1 and 2.

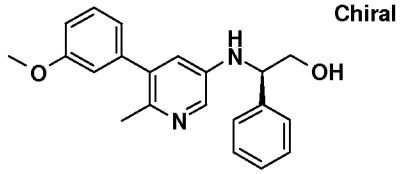
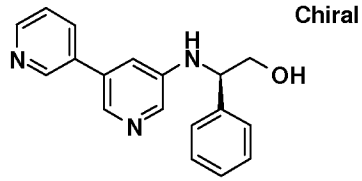
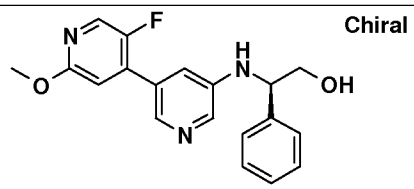
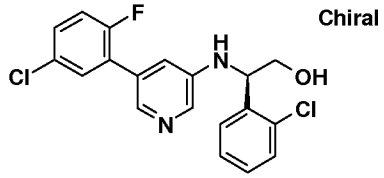
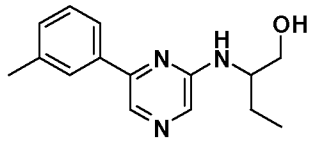
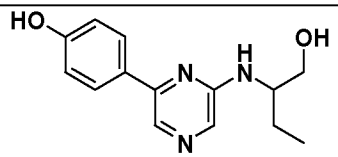
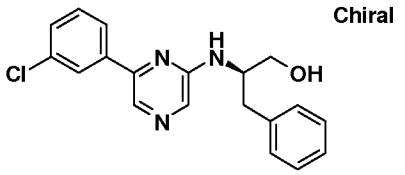
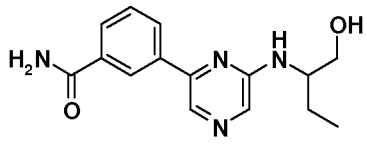
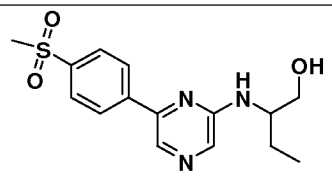
Table 1: Structure, name and activity data of particular compounds

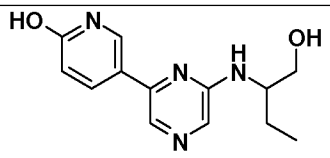
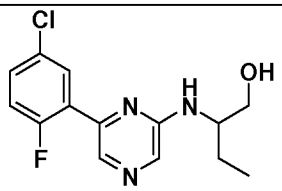
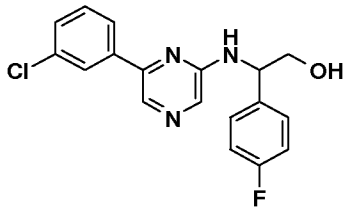
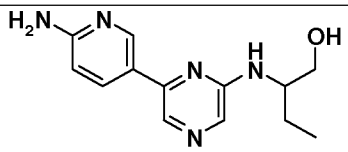
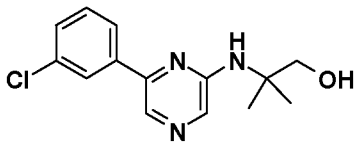
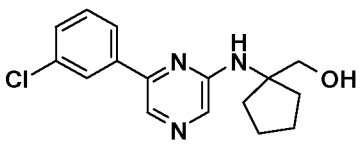
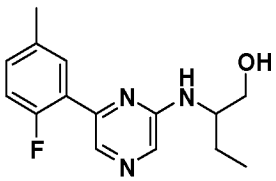
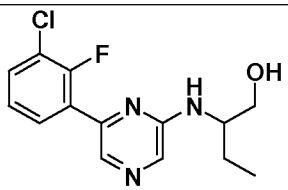
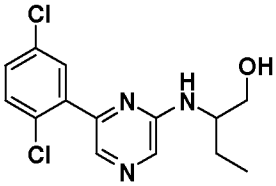
Example No.	Structure	Name	IC_{50} (μM)
1		2-[5-(3-Chloro-phenyl)-pyridin-3-ylamino]-butan-1-ol	0.0133
2		(*R*)-2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol	0.0192
3		(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol	0.0075
4		(*R*)-2-[5-(4-Hydroxy-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol	0.0048
5		{1-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-cyclopentyl}-methanol	0.0261
6		(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.0194
7		(*R*)-2-[5-(2-Fluoro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.0056
8		(*R*)-2-[5-(3-Chloro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.0013
9		4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methyl-phenol	0.0016

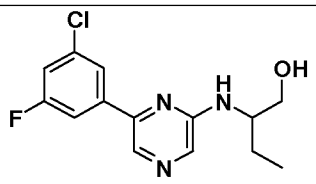
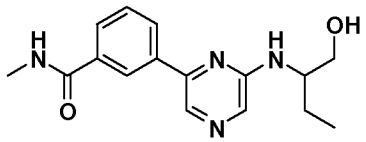
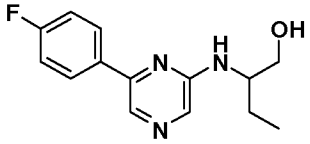
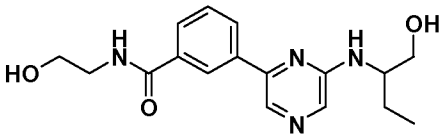
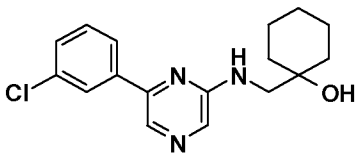
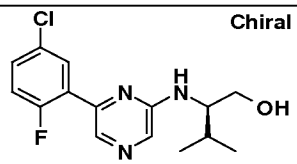
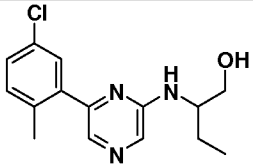
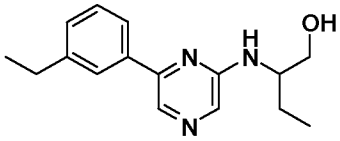
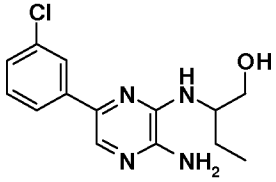
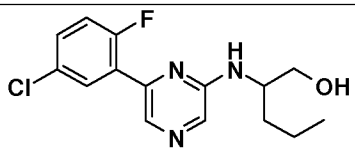
10		2-Fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol	0.0130
11		2-Chloro-5-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol	0.0014
12		(*R*)-2-[5-(3-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.0416
13		(*R*)-2-[5-(4-Chloro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	3.9676
14		(*R*)-2-Phenyl-2-(5-p-tolyl-pyridin-3-ylamino)-ethanol	4.5091
15		(*R*)-2-[5-(4-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	2.1949
16		(*R*)-2-[5-(4-Hydroxymethyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	1.8570
17		(*R*)-2-[5-(3-Amino-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	2.1267
18		2-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol	7.6555

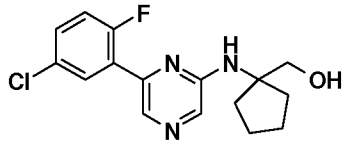
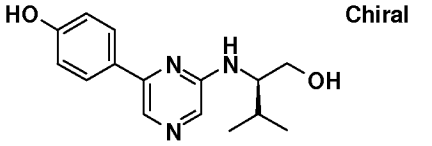
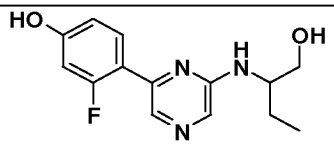
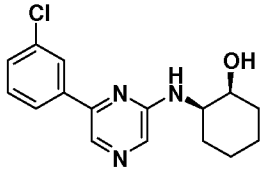
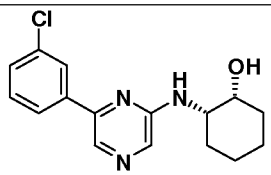
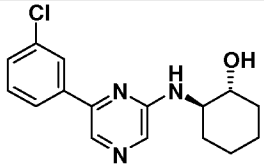
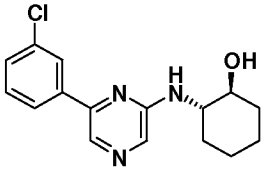
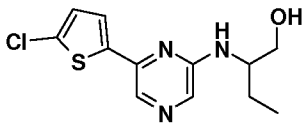
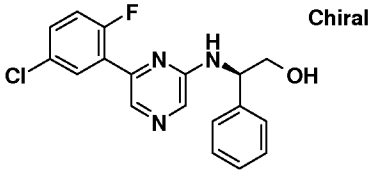
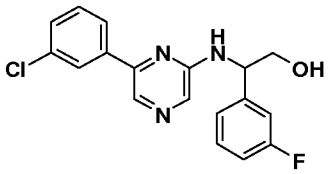
19	 Chiral	(*R*)-2-[5-(4-Methoxy-2-methyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	2.5370
20	 Chiral	4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid	1.6761
21	 Chiral	4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzamide	0.4306
22	 Chiral	(*R*)-2-[5-(3-Chlorophenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.0470
23	 Chiral	4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzonitrile	2.7781
24	 Chiral	(*R*)-2-[5-(4-Fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.4329
25	 Chiral	(*R*)-2-[5-(4-Amino-3-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.1900
26	 Chiral	3-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol	0.3671

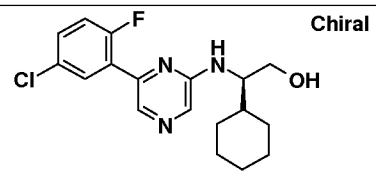
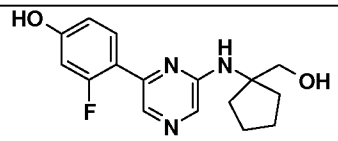
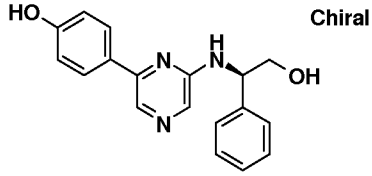
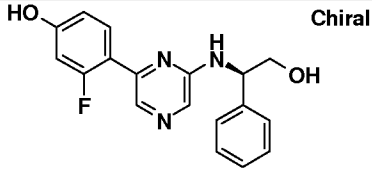
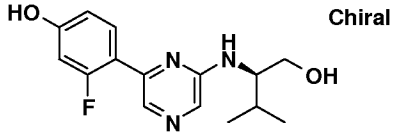
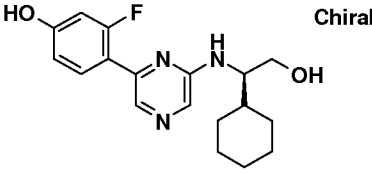
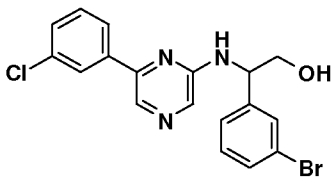
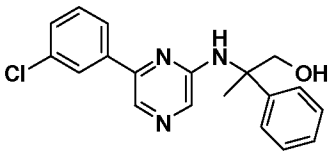
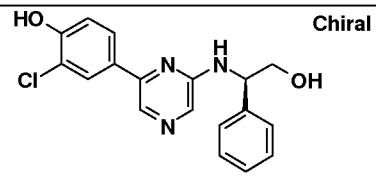
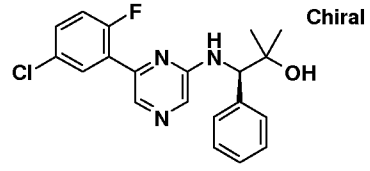
27		(*R*)-2-Phenyl-2-[5-(1H-pyrazol-4-yl)-pyridin-3-ylamino]-ethanol	2.2997
28		(*R*)-2-[5-(5-Chloro-thiophen-2-yl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.3186
29		2-Hydroxy-5-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-enzamide	0.1540
30		(*R*)-2-{[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol	1.3528
31		4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methoxy-phenol	0.0133
32		2-Chloro-4-{5-[((*R*)-2-hydroxy-1-phenyl-ethyl)-methyl-amino]-pyridin-3-yl}-phenol	0.0780
33		(*R*)-2-{[5-(3-Methoxy-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol	1.8243
34		(*R*)-2-Phenyl-2-[5-(3-trifluoromethoxy-phenyl)-pyridin-3-ylamino]-ethanol	1.0744
35		(*R*)-2-[5-(4-Fluoro-3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol	0.6993

36		(*R*)-2-[5-(3-Methoxy-phenyl)-6-methyl-pyridin-3-ylamino]-2-phenyl-ethanol	5.5444
37		(*R*)-2-([3,3']Bipyridinyl-5-ylamino)-2-phenyl-ethanol	2.2545
38		(*R*)-2-(5'-Fluoro-2'-methoxy-[3,4']bipyridinyl-5-ylamino)-2-phenyl-ethanol	0.1803
39		(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-(2-chloro-phenyl)-ethanol	0.0410
40		2-(6-*m*-Tolyl-pyrazin-2-ylamino)-butan-1-ol	1.1440
41		4-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol	0.0187
42		(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-3-phenyl-propan-1-ol	0.3706
43		3-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide	0.1951
44		2-[6-(4-Methanesulfonyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol	2.6430

45		5-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-pyridin-2-ol	1.0290
46		2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	0.0517
47		2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(4-fluoro-phenyl)-ethanol	0.1612
48		2-[6-(6-Amino-pyridin-3-yl)-pyrazin-2-ylamino]-butan-1-ol	5.2900
49		2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol	0.0446
50		{1-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol	0.0186
51		2-[6-(2-Fluoro-5-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol	0.1800
52		2-[6-(3-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	1.6600
53		2-[6-(2,5-Dichloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	4.1530

54		2-[6-(3-Chloro-5-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	4.8570
55		3-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-*N*-methyl-benzamide	0.3191
56		2-[6-(4-Fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	0.6477
57		*N*-(2-Hydroxy-ethyl)-3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide	2.1230
58		1-{[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-methyl}-cyclohexanol	0.1388
59		(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-3-methyl-butan-1-ol	0.0074
60		2-[6-(5-Chloro-2-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol	2.2310
61		2-[6-(3-Ethyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol	5.0760
62		2-[3-Amino-6-(3-chloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol	2.0970
63		2-Chloro-6-(5-chloro-2-fluorophenyl)-pyrazine	0.0376

64		{1-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol	0.0047
65		4-[6-((*R*)-1-Hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol	0.0021
66		3-Fluoro-4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol	0.0083
67		(1*S*, 2*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol	0.5038
68		(1*R*, 2*S*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol	0.2110
69		(1*R*, 2*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol	0.3307
70		(1*S*, 2*S*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol	0.6979
71		2-[6-(5-Chloro-thiophen-2-yl)-pyrazin-2-ylamino]-butan-1-ol	0.0579
72		(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol	0.0052
73		2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(3-fluoro-phenyl)-ethanol	0.0759

74		(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-cyclohexyl-ethanol	1.1922
75		3-Fluoro-4-[6-(1-hydroxymethyl-cyclopentylamino)-pyrazin-2-yl]-phenol	0.0010
76		(*R*)-2-[6-(4-Hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol	0.0055
77		(*R*)-2-[6-(2-Fluoro-4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol	0.0016
78		3-Fluoro-4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol	0.0005
79		4-[6-((*R*)-1-Cyclohexyl-2-hydroxy-ethylamino)-pyrazin-2-yl]-3-fluoro-phenol	0.2591
80		2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(3-bromo-phenyl)-ethanol	0.4405
81		2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-propan-1-ol	0.2542
82		2-Chloro-4-[6-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyrazin-2-yl]-phenol	0.0004
83		(*R*)-1-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-methyl-1-phenyl-propan-2-ol	1.1237

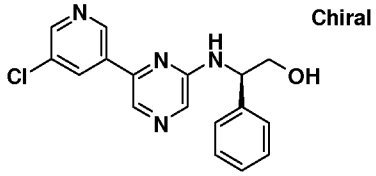
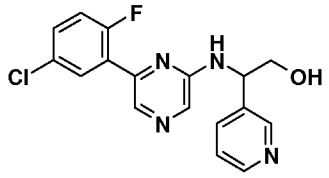
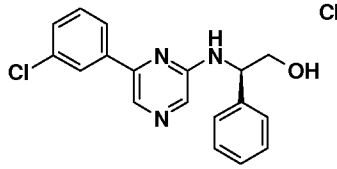
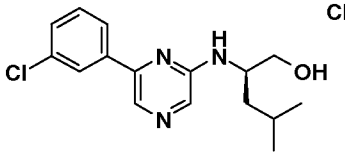
84	 Chiral	(*R*)-2-[6-(5-Chloro-pyridin-3-yl)-pyrazin-2-ylamino]-2-phenyl-ethanol	0.0827
85		2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-pyridin-3-yl-ethanol	0.0868
86	 Chiral	(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol	0.0269
87	 Chiral	(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-4-methyl-pentan-1-ol	0.0514

Table 2: NMR and MS data of particular compounds

Example No.	^{1}H NMR data	MS obsd. (ESI$^+$) [(M+H)$^+$]
1	^{1}H NMR (METHANOL-d$_4$): δ 8.04 - 8.26 (m, 2H), 7.94 (s, 1H), 7.80 (s, 1H), 7.62 - 7.72 (m, 1H), 7.51 - 7.60 (m, 2H), 3.82 (m, 1H), 3.59 - 3.70 (m, 1H), 3.46 - 3.57 (m, 1H), 1.90 - 1.77 (m, 1 H), 1.70 - 1.55 (m, 1 H), 1.05 (t, 3 H)	277.1
2	^{1}H NMR (METHANOL-d$_4$): δ 8.03 - 8.27 (m, 2H), 7.93 (s, 1H), 7.78 (s, 1H), 7.61 - 7.71 (m, 1H), 7.50 - 7.60 (m, 2H), 3.82 (m, 1H), 3.59 - 3.70 (m, 1H), 3.46 - 3.57 (m, 1H), 2.00 (d, 1H), 1.06 (d, 6H)	291.2
3	^{1}H NMR (METHANOL-d$_4$): δ 7.95 - 8.10 (m, 1H), 7.86 (br. s., 1H), 7.52 (m, 1H), 7.42 (m, 1H), 7.16 - 7.31 (m, 2H), 3.67 - 3.76 (m, 1H), 3.63 (d, 1H), 3.36 - 3.38 (m, 1H), 1.91 - 2.09 (m, 1H), 1.04 (d, 6H)	309.2
4	^{1}H NMR (METHANOL-d$_4$): δ 7.90 (br.s, 2H) 7.31 (t, 1H), 7.22 (s, 1H), 6.73 (m, 1H), 6.64 (m, 1H), 3.66 - 3.76 (m, 1H), 3.56 - 3.65 (m, 1H), 2.01 (m, 1H), 1.03 (d, 6H)	291.2
5	^{1}H NMR (METHANOL-d$_4$): δ 8.02 (d, 1H), 7.88 (s, 1H), 7.50 (m, 1H), 7.42 (m, 1H), 7.18 - 7.29 (m, 2H), 3.69 (s, 2H), 1.91 (m, 8H)	321.2
6	^{1}H NMR (METHANOL-d$_4$): δ 7.93 (d, 1H), 7.88 (s, 1H), 7.42 - 7.47 (m, 2H), 7.35 (m, 4H), 7.27 (s, 1H), 7.19 (s, 1H), 7.07 (br. s., 1H), 4.53 (dd, 1H), 3.81 - 3.89 (m, 1H), 3.69 - 3.80 (m, 1H)	343.2

7	^{1}H NMR (METHANOL-d_4): δ 7.78 - 7.91 (m, 2H), 7.40 - 7.49 (m, 2H), 7.36 (t, 2H), 7.22 - 7.31 (m, 1H), 7.15 (t, 1H), 7.06 (s, 1H), 6.67 (m, 1H), 6.59 (m, 1H), 4.51 (dd, 1H), 3.80 - 3.88 (m, 1H), 3.69 - 3.79 (m, 1H)	325.2
8	^{1}H NMR (METHANOL-d_4): δ 7.73 - 8.02 (m, 2H), 7.43 - 7.50 (m, 2H), 7.33 - 7.43 (m, 3H), 7.22 - 7.32 (m, 2H), 7.11 (s, 1H), 6.97 (d, 1H), 4.56 (dd, 1H), 3.81 - 3.91 (m, 1H), 3.71 - 3.81 (m, 1H)	341.1
9	^{1}H NMR (METHANOL-d_4): δ 7.98 - 7.87 (m, 1 H), 7.79 (s, 1 H), 7.51 - 7.43 (m, 2 H), 7.37 (t, 2 H), 7.30 - 7.25 (m, 1H), 7.17 (s, 1 H), 7.15 - 7.05 (m, 2 H), 6.79 (d, 1 H), 4.55 (m, 1 H), 3.91 - 3.83 (m, 1 H), 3.80 - 3.71 (m, 1 H), 2.22 (s, 3H)	321.2
10	^{1}H NMR (METHANOL-d_4): δ 7.94 (s, 1 H), 7.83 (d, 1 H), 7.48 - 7.43 (m, 2 H), 7.37 (t,, 2 H), 7.31 - 7.25 (m, 1H), 7.21 (dd, 1 H), 7.17 - 7.12 (m, 2 H), 6.98 (t, 1 H), 4.56 (dd, 1 H), 3.90 - 3.82 (m, 1 H), 3.80 - 3.73 (m, 1 H)	325.2
11	^{1}H NMR (METHANOL-d_4): δ 7.87 - 7.81 (m, 2 H), 7.47 - 7.41 (m, 2 H), 7.37 (t, 2 H), 7.31 - 7.21 (m, 2 H), 7.04 (s, 1 H), 6.72 (d, 1 H), 4.52 (m, 1 H), 3.88 - 3.82 (m, 1 H), 3.79 - 3.72 (m, 1 H)	359.2
12	^{1}H NMR (METHANOL-d_4): δ 7.96 (s, 1H), 7.89 (d, 1H), 7.44 - 7.48 (m, 2H), 7.23 - 7.40 (m, 4H), 7.12 (s, 1H), 7.03 (d, 1H), 6.92 - 6.96 (m, 2H), 4.55 (dd, 1H), 3.83 - 3.88 (m, 1H), 3.82 (s, 3H), 3.73 - 3.80 (m, 1H)	321.2
13	^{1}H NMR (METHANOL-d_4): δ 7.84 - 8.03 (m, 2H), 7.41 - 7.47 (m, 6H), 7.36 (t, 2H), 7.25 - 7.30 (m, 1H), 7.12 (s, 1H), 4.56 (dd, 1H), 3.82 - 3.88 (m, 1H), 3.74 - 3.80 (m, 1H)	325.1
14	^{1}H NMR (METHANOL-d_4): δ 7.81 - 7.97 (m, 2H), 7.41 - 7.47 (m, 2H), 7.32 - 7.39 (m, 4H), 7.20 - 7.30 (m, 3H), 7.11 (s, 1H), 4.54 (dd, 1H), 3.81 - 3.88 (m, 1H), 3.72 - 3.80 (m, 1H), 2.36 (s, 3H)	305.2
15	^{1}H NMR (METHANOL-d_4): δ 7.94 (s, 1H), 7.83 (br. s., 1H), 7.43 - 7.48 (m, 2H), 7.33 - 7.42 (m, 4H), 7.24 - 7.30 (m, 1H), 7.14 (t, 1H), 6.98 (d, 2H), 4.55 (dd, 1H), 3.84 - 3.88 (m, 1H), 3.83 (s, 3H), 3.74 - 3.79 (m, 1H)	321.2
16	^{1}H NMR (METHANOL-d_4): δ 7.98 (s, 1H), 7.88 (d, 1H), 7.41 - 7.48 (m, 6H), 7.36 (t, 2H), 7.25 - 7.30 (m, 1H), 7.19 (t, 1H), 4.65 (s, 2H), 4.56 (dd, 1H), 3.83 - 3.89 (m, 1H), 3.74 - 3.81 (m, 1H)	321.2
17	^{1}H NMR (METHANOL-d_4): δ 7.92 (s, 1H), 7.84 (d, 1H), 7.43 - 7.48 (m, 2H), 7.36 (t, 2H), 7.23 - 7.31 (m, 1H), 7.09 - 7.19 (m, 2H), 6.84 (s, 1H), 6.74 (t, 2H), 4.54 (dd, 1H), 3.81 - 3.88 (m, 1H), 3.72 - 3.80 (m, 1H)	306.2
18	^{1}H NMR (METHANOL-d_4): δ 7.95 (s, 1H), 7.79 (br. s., 1H), 7.41 - 7.47 (m, 2H), 7.35 (t, 2H), 7.23 - 7.28 (m, 1H), 7.11 - 7.21 (m, 3H), 6.84 - 6.90 (m, 2H), 4.51 (dd, 1H), 3.81 - 3.87 (m, 1H), 3.71 - 3.78 (m, 1H)	307.2

19	^{1}H NMR (METHANOL-d_4): δ 7.90 (br. s., 1H), 7.65 (s, 1H), 7.40 - 7.46 (m, 2H), 7.35 (t, 2H), 7.23 - 7.30 (m, 1H), 7.01 (d, 1H), 6.84 (s, 1H), 6.75 - 6.81 (m, 2H), 4.50 (dd, 1H), 3.82 - 3.87 (m, 1H), 3.80 (s, 3H), 3.72 - 3.78 (m, 1H), 1.99 (s, 3H)	335.2
20	^{1}H NMR (METHANOL-d_4): δ 8.08 (d, 2H), 7.88 - 8.05 (m, 2H), 7.58 (d, 2H), 7.43 - 7.50 (m, 2H), 7.32 - 7.41 (m, 2H), 7.28 (s, 1H), 7.20 (s, 1H), 4.58 (dd, 1H), 3.82 - 3.92 (m, 1H), 3.69 - 3.82 (m, 1H)	335.3
21	^{1}H NMR (METHANOL-d_4): δ 8.01 (s, 1H), 7.86 - 7.98 (m, 3H), 7.57 (d, 2H), 7.41 - 7.49 (m, 2H), 7.36 (t, 2H), 7.28 (d, 1H), 7.17 (t, 1H), 4.57 (dd, 1H), 3.82 - 3.91 (m, 1H), 3.70 - 3.81 (m, 1H)	334.3
22	^{1}H NMR (METHANOL-d_4): δ 7.94 (d, 1H), 7.91 (d, 1H), 7.42 - 7.48 (m, 3H), 7.32 - 7.41 (m, 5H), 7.28 (d, 1H), 7.10 (t, 1H), 4.56 (dd, 1H), 3.82 - 3.90 (m, 1H), 3.72 - 3.81 (m, 1H)	325.1
23	^{1}H NMR (METHANOL-d_4): δ 7.93 - 8.05 (m, 2H), 7.80 (d, 2H), 7.66 (d, 2H), 7.43 - 7.48 (m, 2H), 7.36 (t, 2H), 7.24 - 7.31 (m, 1H), 7.17 (s, 1H), 4.58 (dd, 1H), 3.83 - 3.90 (m, 1H), 3.74 - 3.82 (m, 1H)	316.3
24	^{1}H NMR (METHANOL-d_4): δ 7.94 (d, 1H), 7.88 (d, 1H), 7.42 - 7.50 (m, 4H), 7.36 (t, 2H), 7.24 - 7.30 (m, 1H), 7.10 - 7.20 (m, 3H), 4.56 (dd, 1H), 3.82 - 3.89 (m, 1H), 3.73 - 3.80 (m, 1H)	309.3
25	^{1}H NMR (METHANOL-d_4): δ 7.90 (d, 1 H), 7.80 (d, 1 H), 7.48 - 7.43 (m, 2 H), 7.36 (t, 2 H), 7.30 - 7.25 (m, 1 H), 7.13 - 7.02 (m, 3 H), 6.87 (t, 1 H), 4.54 (m, 1 H), 3.88 - 3.81 (m, 1 H), 3.79 - 3.72 (m, 1 H)	324.2
26	^{1}H NMR (METHANOL-d_4): δ 7.81 - 8.00 (m, 2H), 7.41 - 7.49 (m, 2H), 7.32 - 7.40 (m, 2H), 7.16 - 7.30 (m, 3H), 6.87 - 6.96 (m, 2H), 6.81 (d, 1H), 4.50 - 4.60 (m, 1H), 3.82 - 3.89 (m, 1H), 3.73 - 3.81 (m, 1H)	307.1
27	^{1}H NMR (METHANOL-d_4): δ 7.98 (d, 1H), 7.87 (br. s., 2H), 7.75 (d, 1H), 7.43 - 7.48 (m, 2H), 7.36 (t, 2H), 7.23 - 7.30 (m, 1H), 7.12 (s, 1H), 4.54 (dd, 1H), 3.81 - 3.88 (m, 1H), 3.71 - 3.79 (m, 1H)	281.1
28	^{1}H NMR (METHANOL-d_4): δ 7.96 (s, 1H), 7.85 (d, 1H), 7.42 - 7.47 (m, 2H), 7.38 (t, 2H), 7.25 - 7.32 (m, 1H), 7.15 (d, 1H), 7.09 (s, 1H), 6.99 (d, 1H), 4.53 (dd, 1H), 3.82 - 3.88 (m, 1H), 3.72 - 3.80 (m, 1H)	331.1
29	^{1}H NMR (METHANOL-d_4): δ 8.00 (br. s., 1 H), 7.53 (d, 1 H), 7.46 (m, 3 H), 7.36 (m, 3 H), 7.31 - 7.25 (m, 1 H), 7.19 (br. s., 1 H), 6.99 (m, 1 H), 4.58 (br. s., 1 H), 3.90 - 3.82 (m, 1 H), 3.81 - 3.72 (m, 1 H)	350.2
30	^{1}H NMR (METHANOL-d_4): δ 8.17 (d, 1H), 7.97 (s, 1H), 7.45-7.49 (m, 1H), 7.19 - 7.41 (m, 8H), 5.12 (t, 1H), 4.08 - 4.18 (m, 2H), 2.98 (s, 3H)	357.1
31	^{1}H NMR (METHANOL-d_4): δ 8.17 (s, 1H), 7.84 (d, 1H), 7.76 (s, 1H), 7.45 - 7.51 (m, 2H), 7.40 (t, 2H), 7.29 - 7.36 (m, 1H), 7.03 - 7.09 (m, 2H), 6.91 (d, 1H), 4.67 (dd, 1H), 3.88 - 3.94 (m, 4H), 3.79 - 3.87 (m, 1H)	337.1

32	^{1}H NMR (METHANOL-d_4): δ 7.97 - 8.14 (m, 2H), 7.56 (d, 1H), 7.24 - 7.45 (m, 7H), 7.01 (d, 1H), 5.16 (t, 1H), 4.11 - 4.17 (m, 2H), 3.00 (s, 3H)	355.0
33	^{1}H NMR (METHANOL-d_4): δ 8.13 (d, 1H), 8.06 (d, 1H), 7.22 - 7.43 (m, 7H), 7.15 (d, 1H), 7.09 (s, 1H), 6.93-6.98 (m, 1H), 5.14 (t, 1H), 4.10 - 4.17 (m, 2H), 3.84 (s, 3H), 3.01 (s, 3H)	335.1
34	^{1}H NMR (METHANOL-d_4): δ 7.96 (d, 2 H), 7.58 - 7.43 (m, 4 H), 7.37 (t,, 2 H), 7.34 - 7.25 (m, 3 H), 7.12 (s, 1 H), 4.56 (dd, 1 H), 3.89 - 3.83 (m, 1 H), 3.81 - 3.74 (m, 1 H)	375.2
35	^{1}H NMR (METHANOL-d_4): δ 8.00 - 7.93 (m, 1 H), 7.93 - 7.86 (m, 1 H), 7.46 (d, 2 H), 7.37 (t, 2 H), 7.32 - 7.24 (m, 1 H), 7.18 - 6.98 (m, 4 H), 4.56 (m, 1 H), 3.89 (s, 3 H), 3.87 - 3.83 (m, 1 H), 3.80 - 3.73 (m, 1 H)	339.2
36	^{1}H NMR (DMSO-d_6): δ 7.84 (d, 1H), 7.37 - 7.42 (m, 2H), 7.28-7.34 (m, 3H), 7.19 - 7.25 (m, 1H), 6.91 (dd, 1H), 6.80 (d, 1H), 6.74 (d, 1H), 6.70 (d, 1H), 6.16 (d, 1H), 4.98 (t, 1H), 4.39 - 4.47 (m, 1H), 3.75 (s, 3H), 3.56 - 3.69 (m, 2H), 2.20 (s, 3H)	335.1
37	^{1}H NMR (METHANOL-d_4): δ 8.62 (s, 1H), 8.53 (d, 1H), 7.90 - 8.03 (m, 3H), 7.41 - 7.53 (m, 3H), 7.36 (t, 2H), 7.23 - 7.30 (m, 1H), 7.15 (br. s., 1H), 4.58 (dd, 1H), 3.83 - 3.90 (m, 1H), 3.74 - 3.82 (m, 1H)	292.2
38	^{1}H NMR (METHANOL-d_4): δ 8.06 (d, 1H), 7.98 (d, 1H), 7.95 (s, 1H), 7.42 - 7.46 (m, 2H), 7.36 (t, 2H), 7.24 - 7.30 (m, 1H), 7.13 (br. s., 1H), 6.76 (d, 1H), 4.54 (dd, 1H), 3.92 (s, 3H), 3.82 - 3.88 (m, 1H), 3.72 - 3.81 (m, 1H)	340.3
39	^{1}H NMR (METHANOL-d_4): δ 7.83 - 7.97 (m, 2H), 7.48 - 7.54 (m, 1H), 7.43 - 7.48 (m, 1H), 7.33 - 7.42 (m, 2H), 7.25 - 7.32 (m, 2H), 7.21 (s, 1H), 7.03 (br. s., 1H), 5.02 (dd, J = 7.8, 4.0 Hz, 1H), 3.91 (m, 1H), 3.74 (m, 1H)	377.1
40	^{1}H NMR (METHANOL-d_4): δ 8.11 (s, 1 H), 7.82 (s, 2 H), 7.80 (d, 1 H), 7.37 - 7.31 (m, 1 H), 7.25 (d, 1 H), 3.69 (t, 2 H), 2.43 (s, 1 H), 1.89 - 1.77 (m, 1 H), 1.68 - 1.55 (m, 1 H), 1.05 (t, 3 H)	258.2
41	^{1}H NMR (METHANOL-d_4): δ 8.01 - 8.11 (m, 1H), 7.89 (d, 2H), 7.75 (br. s., 1H), 7.62 - 7.70 (m, 1H), 6.89 (d, 2H), 4.05 - 4.18 (m, 1H), 3.68 (s, 2H), 1.75 - 1.91 (m, 1H), 1.52 - 1.69 (m, 1H), 1.04 (t, 3H)	260.2
42	^{1}H NMR (METHANOL-d_4): δ 8.11 (s, 1H), 8.01 - 8.07 (m, 1H), 7.86 - 7.95 (m, 1H), 7.81 (s, 1H), 7.44 (s, 2H), 7.28 - 7.37 (m, 2H), 7.25 (s, 2H), 7.09 - 7.18 (m, 1H), 4.48 (t, 1H), 3.70 (dd, 2H), 3.01 (d, 1H), 2.84 - 2.95 (m, 1H)	340.2
43	^{1}H NMR (METHANOL-d_4): δ 8.54 (s, 1 H), 8.29 - 8.21 (m, 2 H), 7.95 (d, 1 H), 7.88 (s, 1 H), 7.59 (t, 1 H), 3.69 (m, 2 H), 2.21 (t, 1 H), 2.11 - 2.01 (m, 1 H), 1.69 - 1.56 (m, 1 H), 1.05 (t, 3 H)	287.2
44	^{1}H NMR (METHANOL-d_4): δ 8.31 (d, 2 H), 8.27 (s, 1 H), 8.06 (d, 2 H), 7.93 (s, 1 H), 4.16 (dd, 1 H), 3.75 - 3.62 (m, 2 H), 3.18 (s, 3 H), 1.90 - 1.77 (m, 1 H), 1.70 - 1.55 (m, 1 H), 1.05 (t, 3 H)	322.1

45	^{1}H NMR (METHANOL-d_4): δ 8.27 (dd, 1 H), 8.18 (d, 1 H), 8.02 (s, 1 H), 7.80 (s, 1 H), 6.64 (d, 1 H), 4.08 (dd, 1 H), 3.65 (dd, 2 H), 1.88 - 1.75 (m, 1 H), 1.67 - 1.52 (m, 1 H), 1.03 (t, 3 H)	261.2
46	^{1}H NMR (METHANOL-d_4): δ 8.13 (d, 1 H), 8.04 (dd, 1 H), 7.90 (s, 1 H), 7.49 - 7.40 (m, 1 H), 7.25 (dd, 1 H), 4.11 (m, 1 H), 3.72 - 3.63 (m, 2 H), 1.89 - 1.76 (m, 1 H), 1.62 (m, 1 H), 1.04 (t, 3H)	296.1
47	^{1}H NMR (METHANOL-d_4): δ 8.18 (br. s., 1H), 7.90 - 8.01 (m, 1H), 7.87 (s, 1H), 7.81 (m, 1H), 7.49 (m, 2H), 7.41 (d, 2H), 7.09 (t, 2H), 5.13 (t, 1H), 3.79 - 3.94 (m, 2H)	344.2
48	^{1}H NMR (METHANOL-d_4): δ 8.59 (d, 1 H), 8.12 (dd, 1 H), 8.03 (s, 1 H), 7.76 (s, 1 H), 6.68 (d, 1 H), 4.09 (dd, 1 H), 3.67 (dd, 2 H), 1.90 - 1.74 (m, 1 H), 1.61 (dd, 1 H), 1.03 (t, 3 H)	260.2
49	^{1}H NMR (METHANOL-d_4): δ 8.12 (s, 1H), 7.97 (s, 1H), 7.81 - 7.92 (m, 2H), 7.37 - 7.52 (m, 2H), 3.84 (s, 2H), 1.46 (s, 6H)	278.1
50	^{1}H NMR (METHANOL-d_4): δ 8.15 (s, 1H), 8.00 (s, 1H), 7.86 - 7.95 (m, 2H), 7.40 - 7.52 (m, 2H), 3.93 (s, 2H), 2.05 - 2.15 (m, 2H), 1.96 (d, 2H), 1.83 (br. s., 2H), 1.67 - 1.78 (m, 2H)	304.2
51	^{1}H NMR (METHANOL-d_4): δ 8.08 (d, 1 H), 7.85 (s,1 H), 7.80 (dd, 1 H), 7.28 - 7.22 (m, 1 H), 7.09 (dd, 1 H), 4.09 (dd, 1 H), 3.68 (dd, 2 H), 2.40 (s, 3 H), 1.82 (m, 1 H), 1.68 - 1.55 (m, 1 H), 1.04 (t, 3 H)	276.2
52	^{1}H NMR (METHANOL-d_4): δ 8.09 (d, 1 H), 7.97 - 7.87 (m, 2 H), 7.58 - 7.52 (m, 1 H), 7.30 (t, 1 H), 4.08 (dd, 1 H), 3.74 - 3.60 (m, 2 H), 1.88 - 1.75 (m, 1 H), 1.68 - 1.53 (m, 1 H), 1.03 (t, 3 H)	260.1
53	^{1}H NMR (METHANOL-d_4): δ 7.91 (d, 2 H), 7.61 (d, 1 H), 7.54 - 7.49 (m, 1 H), 7.46 - 7.40 (m, 1 H), 4.08 - 3.97 (m, 1 H), 3.70 - 3.59 (m, 2 H), 1.79 (m, 1 H), 1.66 - 1.54 (m, 1 H), 1.02 (t, 3 H)	313.2
54	^{1}H NMR (METHANOL-d_4): δ 8.18 (s, 1H), 7.90 (s,2 H), 7.77 (d, 1 H), 7.27 (m, 1H), 4.14 (m, 1 H), 3.74 - 3.62 (m,2 H), 1.90 - 1.77 (m, 1 H), 1.68 - 1.54 (m, 2 H), 1.04 (t, 3 H)	296.1
55	^{1}H NMR (METHANOL-d_4): δ 8.47 (s, 1 H), 8.25 - 8.18 (m, 2 H), 7.90 - 7.84 (m, 2 H), 7.58 (t, 1 H), 4.17 (dd, 1 H), 3.69 (m, 2 H), 2.98 (s, 3 H), 1.84 (m, 1 H), 1.62 (dd, 1 H), 1.05 (t, 3 H)	301.2
56	^{1}H NMR (METHANOL-d_4): δ 8.15 - 8.11 (m, 1 H), 8.07 (dd, 2 H), 7.83 (s, 1 H), 7.21 (t, 2 H), 4.13 (dd, 1 H), 3.74 - 3.62 (m, 2 H), 1.90 - 1.77 (m, 1 H), 1.68 - 1.54 (m, 1 H), 1.04 (t, 3 H)	262.2
57	^{1}H NMR (METHANOL-d_4): δ 8.50 (s, 1 H), 8.26 - 8.20 (m, 2 H), 7.94 - 7.85 (m, 2 H), 7.59 (t, 1 H), 4.17 (dd, 1 H), 3.80 - 3.75 (m, 2 H), 3.74 - 3.62 (m, 2 H), 3.59 - 3.54 (m, 2 H), 1.92 - 1.77 (m, 1 H), 1.68 - 1.56 (m, 1 H), 1.05 (t, 3 H)	331.2
58	^{1}H NMR (METHANOL-d_4): δ 8.16 (s, 1H), 8.04 (s, 1H), 7.87 - 7.98 (m, 2H), 7.39 - 7.55 (m, 2H), 3.56 (s, 2H), 1.46 - 1.79 (m, 10H)	318.2

59	^{1}H NMR (METHANOL-d_4): δ 8.12 (d, 1H), 8.04 (dd, 1H), 7.93 (s, 1H), 7.38 - 7.50 (m, 1H), 7.24 (m, 1H), 4.12 (d, 1H), 3.61 - 3.84 (m, 2H), 2.08 (d, 1H), 1.04 (t, 6H)	310.2
60	^{1}H NMR (METHANOL-d_4): δ 7.95 - 7.66 (m, 1 H), 7.39 (d, 1 H), 7.35 - 7.24 (m, 2 H), 4.01 (dd, 1 H), 3.68 - 3.57 (m, 2 H), 2.38 (s, 3 H), 1.87 - 1.72 (m, 1 H), 1.66 - 1.50 (m, 1 H), 1.01 (t, 3 H)	292.1
61	^{1}H NMR (METHANOL-d_4): δ 8.13 (s, 1 H), 7.90 - 7.78 (m, 3 H), 7.43 - 7.35 (m, 1 H), 7.29 (d, 1 H), 4.12 (dd, 1 H), 3.76 - 3.63 (m, 2 H), 2.74 (m, 2 H), 1.90 - 1.76 (m, 1 H), 1.69 - 1.56 (m, 1 H), 1.30 (t, 3 H), 1.05 (t, 3 H)	272.2
62	^{1}H NMR (DMSO-d_6): δ 7.90 (s, 1 H), 7.85 (d, 1 H), 7.80 (s, 1 H), 7.39 (t, 1 H), 7.28 (dd, 1 H), 4.15 - 4.02 (m, 1 H), 3.53 (m, 2 H), 1.83 - 1.68 (m, 1 H), 1.62 - 1.48 (m, 1 H), 0.94 (t, 3 H)	293.1
63	^{1}H NMR (METHANOL-d_4): δ8.13 (d, 1H), 8.05 (dd, 1H), 7.89 (s, 1H), 7.44 (t, 1H), 7.25 (m, 8.8 Hz, 1H), 4.22 (dd, 1H), 3.66 (d, 2H), 1.65 - 1.81 (m, 1H), 1.36 - 1.64 (m, 3H), 1.00 (t, 3H)	310.2
64	^{1}H NMR (METHANOL-d_4): δ 8.12 (d, 1H), 7.97 (dd, 1H), 7.92 (s, 1H), 7.40 - 7.50 (m, 1H), 7.26 (m, 1H), 3.90 (s, 2H), 2.09 (d, 2H), 1.66 - 1.98 (m, 6H)	322.2
65	^{1}H NMR (METHANOL-d_4): δ 8.03 (s, 1H), 7.88 (d, 2H), 7.76 (s, 1H), 6.88 (d, 2H), 4.11 (d, 1H), 3.72 (dd, , 2H), 2.08 (d, 1H), 1.04 (t, 6H)	274.3
66	^{1}H NMR (METHANOL-d_4): δ 8.02 (s, 1 H), 7.88 (t, 1 H), 7.74 (s, 1 H), 6.70 (dd, 1 H), 6.58 (dd, 1 H), 4.05 (m, 1 H), 3.73 - 3.58 (m, 2 H), 1.79 (m, 1 H), 1.59 (m, 1 H), 1.01 (t, 3 H)	278.2
67	^{1}H NMR (METHANOL-d_4): δ 8.15 (s, 1 H), 8.05 (s, 1 H), 7.94 (d, 1 H), 7.88 (s, 1 H), 7.50 - 7.42 (m, 2 H), 3.93 - 3.83 (m, 1H), 3.55 (m, 1 H), 2.25 - 2.14 (m, 1 H), 2.12 - 2.01 (m, 1 H), 1.85 - 1.73 (m, 2 H), 1.53 - 1.28 (m, 4 H)	304.1
68	^{1}H NMR (METHANOL-d_4): δ 8.15 (s, 1 H), 8.05 (s, 1 H), 7.94 (d, 1 H), 7.88 (s, 1 H), 7.50 - 7.42 (m, 2 H), 3.93 - 3.83 (m, 1H), 3.55 (m, 1 H), 2.25 - 2.14 (m, 1 H), 2.12 - 2.01 (m, 1 H), 1.85 - 1.73 (m, 2 H), 1.53 - 1.28 (m, 4 H)	304.1
69	^{1}H NMR (METHANOL-d_4): δ 6.62 (s, 1 H), 6.49 (s, 1 H), 6.42 - 6.37 (m, 2 H), 5.97 - 5.88 (m, 2 H), 2.60 (d, 2 H), 1.84 - 1.77 (m, 2 H), 0.40 - 0.30 (m, 2 H), 0.27 - 0.12 (m, 2 H), 0.01 - 0.09 (m, 2 H)	304.1
70	^{1}H NMR (METHANOL-d_4): δ 6.62 (s, 1 H), 6.49 (s, 1 H), 6.42 - 6.37 (m, 2 H), 5.97 - 5.88 (m, 2 H), 2.60 (d, 2 H), 1.84 - 1.77 (m, 2 H), 0.40 - 0.30 (m, 2 H), 0.27 - 0.12 (m, 2 H), 0.01 - 0.09 (m, 2 H)	304.1
71	^{1}H NMR (METHANOL-d_4): δ 8.05 (s, 1 H), 7.76 (s, 1 H), 7.50 (d, 1 H), 7.00 (d, 1 H), 4.00 (m, 1 H), 3.72 - 3.62 (m, 2 H), 1.80 (m, 1 H), 1.68 - 1.55 (m, 1 H), 1.03 (t, 3 H)	284.1

72	^{1}H NMR (METHANOL-d_4): δ 8.15 (d, 1H), 7.97 (s, 1H), 7.75 (dd, 1H), 7.47 (d, 2H), 7.37 (t, 3H), 7.26 (s, 1H), 7.18 (m, 1H), 5.07 (dd, 1H), 3.80 - 3.95 (m, 2H)	344.3
73	^{1}H NMR (METHANOL-d_4): δ 8.19 (s, 1 H), 7.96 (s, 1 H), 7.87 (s, 1 H), 7.83 - 7.78 (m, 1 H), 7.44 - 7.35 (m, 3 H), 7.33 - 7.28 (m, 1 H), 7.22 (d, 1 H), 6.99 (m, 1 H), 5.15 (t, 1 H), 3.94 - 3.83 (m, 2 H)	344.1
74	^{1}H NMR (METHANOL-d_4): δ 8.67 (d, 1 H), 8.29 (s, 1 H), 8.10 (dd, 1 H), 7.57 - 7.49 (m, 1 H), 7.32 (m, 1 H), 5.37 (m, 1 H), 4.68 (m, 1 H), 4.33 (dd, 1 H), 3.07 (m, 1 H), 2.21 (t, 1 H), 2.05 (d, 1 H), 1.95 - 1.79 (m, 2 H), 1.73 (d, 1 H), 1.65 - 1.52 (m, 2 H), 1.38 - 1.28 (m, 1H), 1.26 - 1.11 (m, 2 H)	350.1
75	^{1}H NMR (METHANOL-d_4): δ δ 8.03 (d, 1 H), 7.83 - 7.75 (m, 2 H), 6.70 (dd, 1 H), 6.57 (dd, 1 H), 3.88 (s, 2 H), 2.11 - 2.02 (m, 3 H), 1.98 - 1.89 (m, 2 H), 1.85 - 1.78 (m, 2 H), 1.73 (d, 2 H)	304.2
76	^{1}H NMR (METHANOL-d_4): δ 8.07 (s, 1H), 7.73 - 7.82 (m, 3H), 7.47 (d, 2H), 7.36 (t, 2H), 7.27 (d, 1H), 6.83 (d, 2H), 5.15 (t, 1H), 3.82 - 3.93 (m, 2H)	308.3
77	^{1}H NMR (METHANOL-d_4): δ 8.07 (d, 1H), 7.81 (s, 1H), 7.63 - 7.74 (m, 1H), 7.46 (d, 2H), 7.32 - 7.40 (m, 2H), 7.27 (d, 1H), 6.66 (dd, 1H), 6.58 (dd, 1H), 5.12 (t, 1H), 3.87 (dd, 2H)	326.2
78	^{1}H NMR (METHANOL-d_4): δ 8.10 (s, 1H), 7.90 (t, 1H), 7.81 (s, 1H), 6.74 (dd, 1H), 6.61 (dd, 1H), 4.08 (d, 1H), 3.72 (dd, 2H), 1.99 - 2.15 (m, 1H), 1.04 (t, 6H)	292.3
79	^{1}H NMR (METHANOL-d_4): δ 8.56 (d, 1 H), 8.14 (s, 1 H), 7.96 (t, 1 H), 6.77 (dd, 1 H), 6.65 (dd, 1 H), 5.36 (t, 1H), 4.64 (dd, 1 H), 4.43 - 4.34 (m, 1 H), 2.21 (t, 2 H), 2.05 (d, 2 H), 1.62 (br. s., 2 H), 1.40 - 1.28 (m, 5 H)	332.2
80	^{1}H NMR (METHANOL-d_4): δ 8.20 (s, 1 H), 7.96 (s, 1 H), 7.87 (s, 1 H), 7.83 - 7.77 (m, 1 H), 7.67 (s, 1 H), 7.49 - 7.36 (m, 4 H), 7.31 - 7.21 (m, 1 H), 5.10 (t, 1 H), 3.88 (dd, 2 H)	405.1
81	^{1}H NMR (METHANOL-d_4): δ 8.10 (s, 1 H), 7.89 (s, 1 H), 7.58 - 7.48 (m, 3 H), 7.45 (s, 1 H), 7.39 - 7.29 (m, 4 H), 7.26 - 7.19 (m, 1 H), 4.07 (d, 1 H), 3.83 (d, 1 H), 1.81 (s, 3 H)	340.1
82	^{1}H NMR (METHANOL-d_4): δ 7.97 - 8.14 (m, 2H), 7.56 (d, 1H), 7.24 - 7.45 (m, 6H), 7.01 (d, 1H), 6.83 (d, 2H), 5.15 (t, 1H), 3.82 - 3.93 (m, 2H)	342.1
83	^{1}H NMR (METHANOL-d_4): δ 8.12 (d, 1 H), 8.03 (s, 1 H), 7.77 (dd, 1 H), 7.50 (d, 2 H), 7.40 (m, 1 H), 7.35 (t, 2 H), 7.28 - 7.15 (m, 2 H), 4.92 (s, 1 H), 1.37 (s, 3 H), 1.22 (s, 3 H)	372.1
84	^{1}H NMR (METHANOL-d_4): δ 8.97 (d, 1 H), 8.56 (d, 1 H), 8.33 - 8.24 (m, 2 H), 8.03 (s, 1 H), 7.47 (d, 2 H), 7.37 (t, 2 H), 7.30 - 7.23 (m, 1 H), 5.16 - 5.08 (m, 1 H), 3.95 - 3.84 (m, 2 H)	327.1
85	^{1}H NMR (METHANOL-d_4): δ 8.66 (d, 1 H), 8.45 (d, 1 H), 8.19 (d, 1 H), 8.04 (s, 1 H), 7.95 (d, 1 H), 7.67 (dd, 1 H), 7.45 (dd, 1 H), 7.40 (m, 1 H), 7.20 (dd, 1 H), 5.16 (t, 1 H), 3.94 (d, 2 H)	345.1

86	^{1}H NMR (CHLOROFORM-d): δ 8.19 (s, 1 H), 8.05 (s, 1 H), 7.83 (s, 1 H), 7.73 (d, 1 H), 7.53 - 7.36 (m, 7 H), 5.11 (br. s., 1 H), 4.14 - 3.95 (m, 2 H)	326.2
87	^{1}H NMR (METHANOL-d_4): δ 8.15 (s, 1 H), 8.07 (s, 1 H), 7.96 - 7.89 (m, 1 H), 7.85 (s, 1 H), 7.52 - 7.37 (m, 2 H), 4.37 (m, 1H), 3.64 (m, 2 H), 1.80 (m, 1 H), 1.55 (t, 2 H), 1.00 (m, 6 H)	306.2

More particular compounds of formula I include the following:

(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

(*R*)-2-[5-(2-Fluoro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

(*R*)-2-[5-(3-Chloro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methyl-phenol;

2-Fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;

2-Chloro-5-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;

(*R*)-2-[5-(3-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

(*R*)-2-[5-(3-Chlorophenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methoxy-phenol;

(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

(*R*)-2-[6-(4-Hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

(*R*)-2-[6-(2-Fluoro-4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol; and

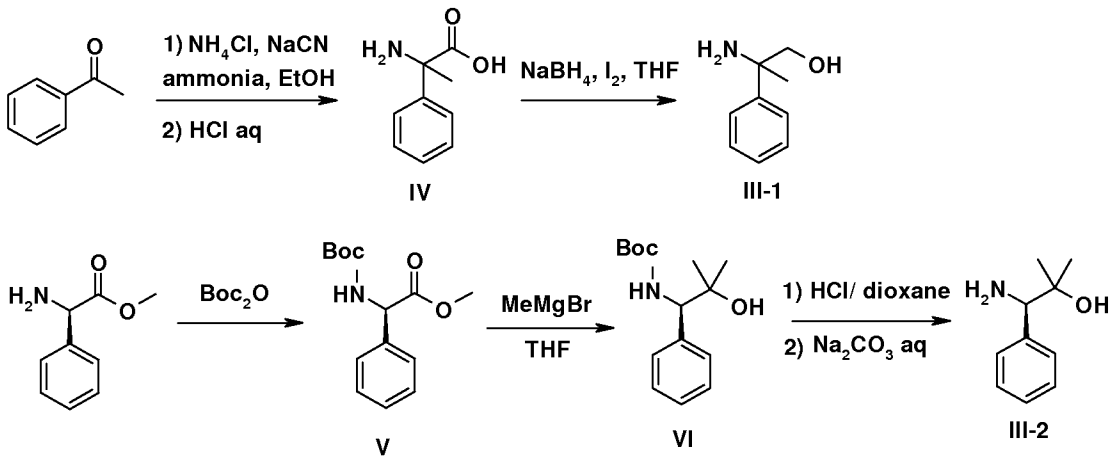
2-Chloro-4-[6-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyrazin-2-yl]-phenol.

SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and W are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic route for intermediate (Scheme 1)

Scheme 1



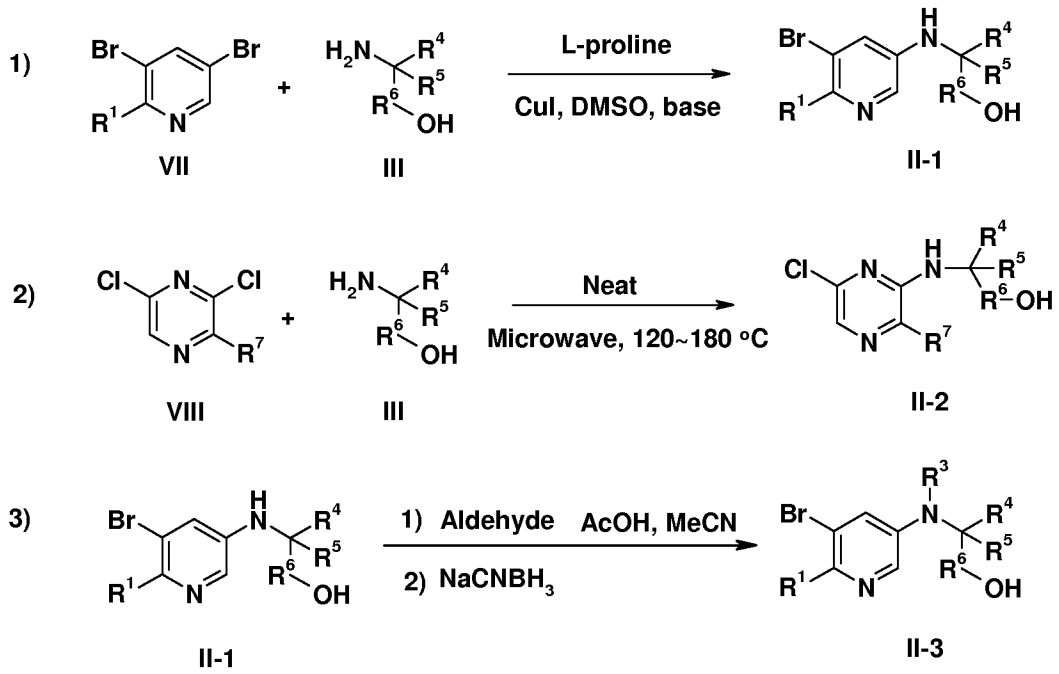
Intermediates **III-1** and **III-2** can be prepared according to Scheme 1.

Intermediate **IV** can be synthesized via Strecker reaction among 1-Phenyl-ethanone, cyanurede sodium and ammonium chlorid in ammonia/EtOH solution followed by hydrolysis reaction in HCl aqueous solution. Reduction intermediate **IV** by sodiumborohydride and iodine in THF affords Intermediate **III-1**.

Protect amino group of (*R*)-amino-phenyl-acetic acid methyl ester with Boc_2O affords intermediate **V**. Intermediate **VI** can be synthesized via Grignard reaction between intermediate **V** and methyl magnesium bromide in THF. Deprotection of Boc group of intermediate **VI** affords intermediate **III-2**.

General synthetic route for intermediate (Scheme 2)

Scheme 2



Intermediates **II-1** to **II-3** can be prepared according to Scheme 2.

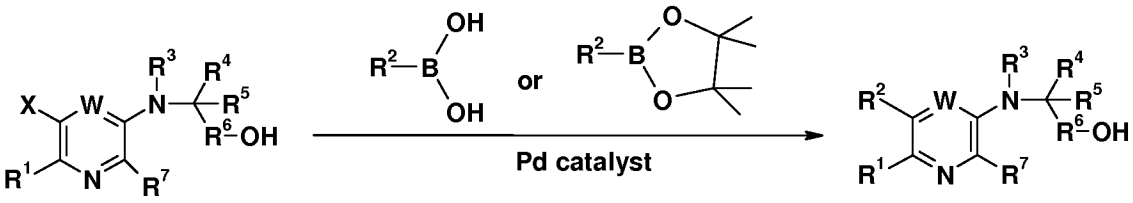
By **Method 1**), coupling between substituted 3, 5-dibromo-pyridine **VII** and compound **III** affords intermediate **II-1**. The reaction can be carried out in the presence of copper catalyst, and a ligand such as dimethylamino acetic acid or *L*-proline, and a suitable base such as K_2CO_3 or Cs_2CO_3, in a suitable solvent such as DMSO or 1,4-dioxane.

By **Method 2),** neat reaction between substituted 2,6-dichloro-pyrazine **VIII** and compound **III** under microwave at 120 ~180 °C affords intermediate **II-2**.

By **Method 3),** Intermediate **II-3** can be synthesized via reductive amination reaction between compound **II-1** and aldehyde. Intermediate **II-1** mixes with aldehyde first in MeCN/AcOH, followed by reduction reaction in the presence of $NaCNBH_3$ affords intermediate **II-3**.

General synthetic route for formula **Ia** (Scheme 3)

Scheme 3



II

Ia

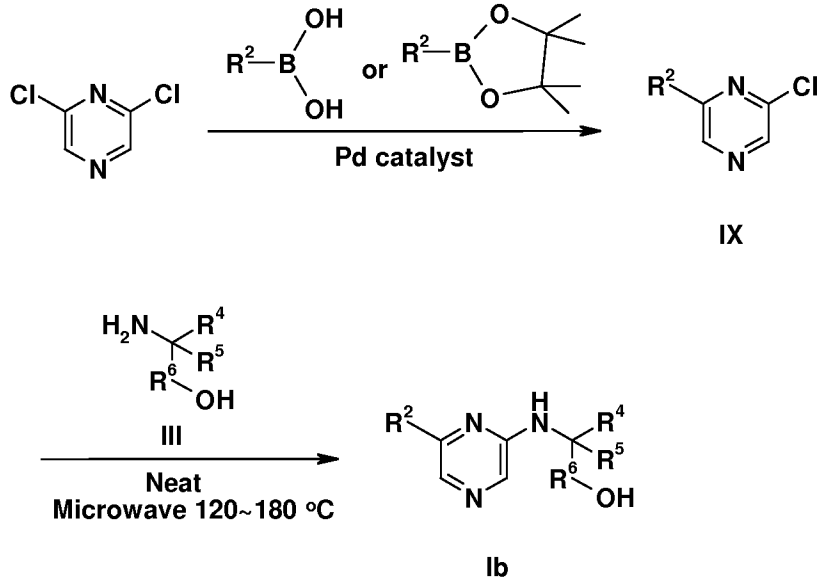
X is chloro, bromo or iodo.

The compound of formula **Ia** can be prepared according to Scheme 3.

Coupling between compound **II** and boronic acid or boronic ester affords **Ia**. The reaction can be carried out in the presence of Pd catalyst such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, and a suitable base such as K_3PO_4, Na_2CO_3, K_2CO_3 or Cs_2CO_3, in a suitable solvent such as DME/H_2O, 1,4-dioxane/H_2O or DMF/H_2O.

General synthetic route for formula **Ib** (Scheme 4)

Scheme 4



IX

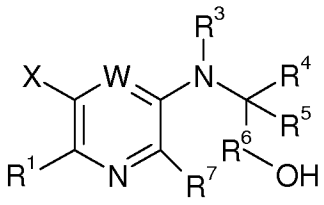
Ib

The compound of formula **Ib** can be prepared according to Scheme 4.

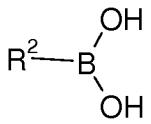
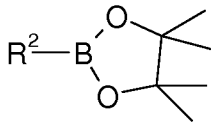
Coupling between 2,6-dichloro-pyrazine and boronic acid or boronic ester affords intermediate **IX** . The reaction can be carried out in the presence of Pd catalyst such as $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, and a suitable base such as K_3PO_4, Na_2CO_3, K_2CO_3 or Cs_2CO_3, in a suitable solvent such as DME/H_2O, 1,4-dioxane/H_2O or DMF/H_2O. Neat reaction between intermediate **IX** and compound **III** under microwave at 120 ~180 °C affords intermediate **Ia**.

This invention also relates to a process for the preparation of a compound of formula I comprising the reaction of

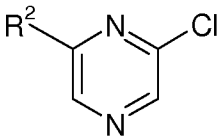
(a) a compound of formula (A)



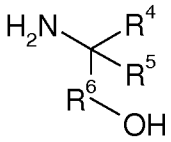
(A)

with  or  in the presence of a catalyst and a base;

(b) a compound of formula (B)



(B)

with  under microwave;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and W are defined above unless otherwise indicated; X is chloro, bromo or iodo.

In step (a), the catalyst can be for example $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, the base can be for example K_3PO_4, Na_2CO_3, K_2CO_3 or Cs_2CO_3.

A compound of formula I when manufactured according to the above process is also an object of the invention.

PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

The invention also relates to a compound of formula I for use as therapeutically active substance.

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of formula I may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but particularly ranges anywhere from about 3 to about 8. In one example, a compound of formula I is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds of formula I are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit CDK8 activity. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.1 to 50 mg/kg of patient body weight per day, with the typical initial range of compound used being about 0.3 to about 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, preferably contain from about 5 mg to about 500 mg of the compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components

conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., 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. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 5 mg to 500 mg of the compound of the invention compounded with about 90 mg to 30 mg anhydrous lactose, about 5 mg to 40 mg sodium croscarmellose, about 5 mg to 30 mg polyvinylpyrrolidone (PVP) K30, and about 1 mg to 10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5mg to 400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formula I, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

Another embodiment includes a pharmaceutical composition comprising a compound of Formula I for use in the treatment of a hyperproliferative disease. Another embodiment includes

a pharmaceutical composition comprising a compound of Formula I for use in the treatment of cancer.

INDICATIONS AND METHODS OF TREATMENT

The compounds of the invention inhibit the kinase activity of protein. Accordingly, the compounds of the invention are useful for inhibiting cell proliferation and inducing cell cycle arrest and apoptosis in particular cancer cells.

Compounds of the invention are useful for inhibiting cell proliferation, inducing cell cycle arrest and apoptosis in cells that overexpress CDK8 or Cyclin C.

Alternatively, compounds of the invention are useful for inhibiting cell proliferation, inducing cell cycle arrest and apoptosis in cells in which the apoptotic pathway is disrupted or proliferation pathway is overexpressed/or immortalized, for example by deregulation of CDK8 or Cyclin C.

The compounds of inventions are useful as inhibitors of CDK8 or Cyclin C.

An embodiment of this invention includes the use of a compound for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers. A further embodiment of this invention includes the use of a compound for the treatment of gastric cancer or colorectal cancer.

Another embodiment of this invention includes the use of a compound for the preparation of a medicament for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers.

A further embodiment of this invention includes the use of a compound for the preparation of a medicament for the treatment of gastric cancer or colorectal cancer.

Another embodiment of this invention relates to a compound of formula I for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers.

A further embodiment of this invention relates to a compound of formula I for the treatment of gastric cancer or colorectal cancer.

Another embodiment includes a method of treating or preventing cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof. Particular cancers for treatment or prevention include bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers. More particularly, the invention relates to a method of treating or preventing gastric cancer or colorectal cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof. Another embodiment includes a method of treating or preventing neurodegenerative disease in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof. Particular neurodegenerative disease for treatment includes Alzhemers disease, parkinson's disease, Huntington's dsease and Amyotrophic lateral sclerosis (ALS).

COMBINATION THERAPY

The compounds of the invention can be used in combination with small molecule inhibitors such as tyrosine kinase inhibitors, Serine/Threonine kinase inhibitors, lipid kinase inhibitors, protein-protein inhibitors, etc., cytotoxic agents, radiotherapy, antibodies and cancer vaccines for the treatment of cancer.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations used herein are as follows:

µL:	microliter
µm:	micrometer
µM:	micromoles per liter
AcOH:	acetic acid
Ar:	argon
Boc:	formic acid *tert*-butyl ester
Boc_2O:	bis(1,1-dimethylethyl)dicarbonate
BSA:	bovine serum albumin
n-BuOH:	n-Butyl alcohol
CCK-8:	Cell Counting Kit-8
CHLOROFORM-d:	deuterotrichloromethane
DCM:	dichloromethane
DME:	1,2-dimethoxyethane
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
DMSO-d_6:	deuterated dimethylsulfoxide
DTT:	dithiothreitol
EtOAc:	ethyl acetate
EtOH:	ethanol
EGTA:	ethylene glycol tetraacetic acid
g:	gram
IC_{50}:	the half maximal inhibitory concentration
HATU:	2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCMV:	human cytomegalovirus virus
HIV:	human immunodeficiency
HSV:	herpes simplex virus
HPV:	human papillomavirus
HPLC:	high performance liquid chromatography
LC-MS:	Liquid chromatography/mass spectrometry
MeCN:	acetonitrile
MeOH:	methanol
METHANOL-d_4:	perdeuteromethanol

M:	molarity
mg:	milligram
MHz:	megahertz
mins:	minutes
mL:	milliliter
mM:	millimoles per liter
mm:	millimeter
mmol:	millimole
MS (ESI):	mass spectroscopy (electron spray ionization)
$NaBH_4$:	sodium boranate
$NaCNBH_3$:	sodium cyanoborohydride
nM:	nanomoles per liter
nm:	nanometer
NMR:	nuclear magnetic resonance
obsd.:	observed
OD:	optical density
$Pd(PPh_3)_4$:	tetrakis(triphenylphosphine)palladium
$Pd(PPh_3)_2Cl_2$:	bis(triphenylphosphine)palladium(II) chloride
PE:	petroleum ether
Prep HPLC:	preparative high performance liquid chromatography
THF:	tetrahydrofurane
TR-FRET:	time resolved-fluorescence resonance energy transfer
δ:	chemical shift

General Experimental Conditions

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel Brand and pore size: i) KP-SIL 60 Å, particle size: 40-60 μM; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using X Bridge™ Perp C_{18} (5 µm, OBD™ 30 × 100 mm) column or SunFire™ Perp C_{18} (5 µm, OBD™ 30 × 100 mm) column.

LC/MS spectra were obtained using a MicroMass Plateform LC (Waters™ alliance 2795-ZQ2000). Standard LC/MS conditions were as follows (running time 6 minutes): Acidic condition: A: 0.1% formic acid in H_2O; B: 0.1% formic acid in acetonitrile;

Basic condition: A: 0.01% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Neutral condition: A: H_2O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion $(M+H)^+$.

The microwave assisted reactions were carried out in a Biotage Initiator Sixty.

NMR Spectra were obtained using Bruker Avance 400MHz.

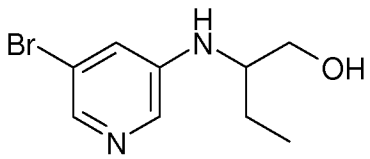
All reactions involving air-sensitive reagents were performed under an argon atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

The following examples were prepared by the general methods outlined in the schemes above. They are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention.

PREPARATIVE EXAMPLES

Example 1: Preparation of 2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-butan-1-ol

Step 1: Preparation of 2-(5-bromo-pyridin-3-ylamino)-butan-1-ol



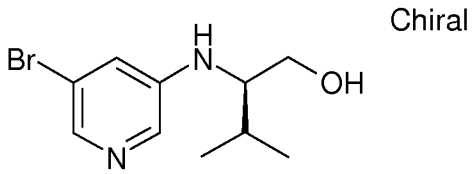
To a solution of 3, 5-dibromopyridine (1.2 g, 5 mmol) in DMSO (20 mL) was added 2-amino-butan-1-ol (712 mg, 8 mmol), CuI (95 mg, 0.5 mmol), K_2CO_3 (1.38 g, 10 mmol) and L-proline (115 mg, 1 mmol). The resulting mixture was degassed and then stirred overnight at 100 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 2:1) to give 2-(5-bromo-pyridin-3-ylamino)-butan-1-ol (500 mg) as yellow oil.

Step 2: Preparation of 2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(5-bromo-pyridin-3-ylamino)-butan-1-ol (122 mg, 0.5 mmol), 3-chloro-phenyl-boronic acid (94 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (25 mg) and potassium carbonate (138 mg, 1 mmol) in DME/H_2O (5:1, 4.5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-butan-1-ol (30 mg).

Example 2: Preparation of (*R*)-2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol

Step 1: Preparation of (*R*)-2-(5-bromo-pyridin-3-ylamino)-3-methyl-butan-1-ol



To a solution of 3, 5-dibromopyridine (1.2 g, 5 mmol) in DMSO (20 mL) was added (*R*)-2-amino-3-methyl-butan-1-ol (0.82 g, 8 mmol), CuI (95 mg, 0.5 mmol), K_2CO_3 (1.38 g, 10 mmol) and L-proline (115 mg, 1 mmol). The resulting mixture was degassed and then stirred overnight at 100 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 2:1) to give (*R*)-2-(5-bromo-pyridin-3-ylamino)-3-methyl-butan-1-ol (500 mg) as yellow oil.

Step 2: Preparation of (*R*)-2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-3-methyl-butan-1-ol (130 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 3-chlorophenylboronic acid (94 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol (30 mg).

Example 3: Preparation of (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol

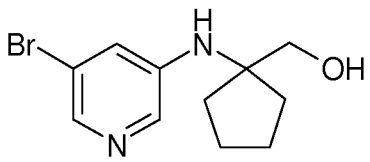
To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-3-methyl-butan-1-ol (130 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 5-chloro-2-fluorophenylboronic acid (104 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After the reaction was completed as monitored by LC-MS, the reaction mixture was cooled to room temperature and then diluted with water (50 mL). The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol (25 mg).

Example 4: Preparation of (*R*)-2-[5-(4-hydroxy-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-3-methyl-butan-1-ol (130 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 4-hydroxy-2-fluorophenylboronic acid (103 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After the reaction was completed as monitored by LC-MS, the mixture was cooled to room temperature, and then diluted with water (50 mL). The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-hydroxy-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol (20 mg).

Example 5: Preparation of {1-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-cyclopentyl}-methanol

Step 1: Preparation of [1-(5-bromo-pyridin-3-ylamino)-cyclopentyl]-methanol



To a solution of 3, 5-dibromopyridine (1.2 g, 5 mmol) in DMSO (20 mL) was added (1-amino-cyclopentyl)-methanol (0.92 mg, 8 mmol), CuI (95 mg, 0.5 mmol), K_2CO_3 (1.38 g, 10

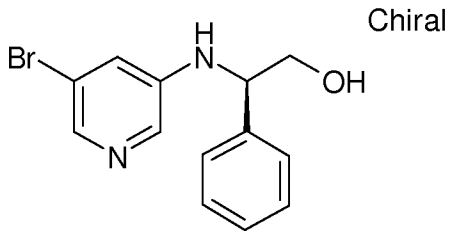
mmol) and L-proline (115 mg, 1 mmol). The resulting mixture was degassed and then stirred overnight at 100 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE=2:1) to give [1-(5-bromo-pyridin-3-ylamino)-cyclopentyl]-methanol (450 mg).

Step 2: Preparation of {1-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-cyclopentyl}-methanol

To a solution of [1-(5-bromo-pyridin-3-ylamino)-cyclopentyl]-methanol (135 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 5-chloro-2-fluorophenylboronic acid (104 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. The mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give {1-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-cyclopentyl}-methanol (26 mg).

Example 6: Preparation of (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Step 1: Preparation of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol



To a solution of 3, 5-dibromopyridine (2.4 g, 10 mmol) in DMSO (45 mL) was added D-phenylglycinol (2.2 g, 16 mmol), CuI (190 mg, 1.0 mmol), K_2CO_3 (2.76 g, 20 mmol) and L-proline (230 mg, 2.0 mmol). The resulting mixture was degassed and then stirred overnight at 100 °C under an Ar atmosphere. After the reaction was completed as monitored by LC-MS, the mixture was cooled to room temperature, and then diluted with water (75 mL). The mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE=1:1) to give (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol

(1.2 g) as a white solid.

Step 2: Preparation of (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (145 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 5-chloro-2-fluorophenylboronic acid (104 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (40 mg).

Example 7: Preparation of (*R*)-2-[5-(2-fluoro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (145 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 2-fluoro-4-hydroxyphenylboronic acid (94 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(2-fluoro-4hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (8 mg).

Example 8: Preparation of (*R*)-2-[5-(3-chloro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (145 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 3-chloro-4-hydroxyphenylboronic acid (103 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-chloro-4hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (25 mg).

Example 9: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methyl-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 4-iodo-2-methyl-Phenol (48 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methyl-phenol (4 mg).

Example 10: Preparation of 2-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 4-bromo-2-fluorophenol (40 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol (9 mg).

Example 11: Preparation of 2-chloro-5-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 4-bromo-2-chloro-5-fluoro-phenol (52 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4 mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-chloro-5-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol (13 mg).

Example 12: Preparation of (*R*)-2-[5-(3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.51 mmol), 3-methoxyphenylboronic acid (156 mg, 1.02 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was heated at 95 °C overnight, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (84 mg).

Example 13: Preparation of (*R*)-2-[5-(4-chloro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-chlorophenylboronic acid (80 mg, 0.514 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was heated at 95 °C overnight, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-chloro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (61 mg).

Example 14: Preparation of (*R*)-2-Phenyl-2-(5-p-tolyl-pyridin-3-ylamino)-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-methylbenzeneboronic acid (140 mg, 1.027 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was heated at 95 °C overnight, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-phenyl-2-(5-p-tolyl-pyridin-3-ylamino)-ethanol (35 mg).

Example 15: Preparation of (*R*)-2-[5-(4-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-methoxybenzeneboronic acid (156 mg, 1.027 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated, and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (73 mg).

Example 16: Preparation of (*R*)-2-[5-(4-hydroxymethyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-(hydroxymethyl)benzeneboronic acid (94 mg, 0.616 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-hydroxymethyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (77 mg).

Example 17: Preparation of (*R*)-2-[5-(3-amino-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 3-aminobenzeneboronic acid (84 mg, 0.616 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-amino-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (37 mg).

Example 18: Preparation of 2-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol

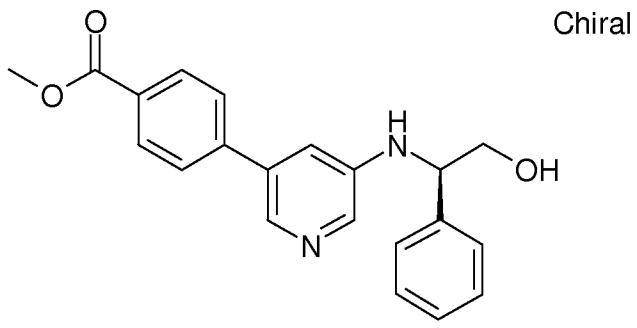
Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 2-hydroxyphenylboronic acid (106 mg, 0.77 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol (37 mg).

Example 19: Preparation of (*R*)-2-[5-(4-methoxy-2-methyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-methoxy-2-methylphenylboronic acid (170 mg, 1.027 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-methoxy-2-methyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (90 mg).

Example 20: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid

Step 1: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid methyl ester



To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (1.2 g, 4 mmol) in DME/H_2O (5:1, 60 mL) was added $Pd(PPh_3)_4$ (924 mg, 0.8 mmol), K_2CO_3 (1.1 g, 8.0 mmol) and 4-methoxycarbonylphenylboronic acid (0.86 g, 4.8 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 2:1) to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid methyl ester (1.0 g) as a white solid

Step 2: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid

To a solution of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid methyl ester (1.0 g, 3 mmol) in MeOH/H_2O (10:1, 22 mL) was added lithium hydroxide (0.63 g, 15 mmol). The resulting mixture was stirred overnight at room temperature. After the reaction was completed as monitored by LC-MS, the mixture was diluted with water (100 mL) and then adjust the PH of the solution to PH 6 with 2.0 M HCl. The mixture was stirred for 30 mins and then extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by chromatography column (DCM / MeOH = 20:1) to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid (560 mg).

Example 21: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzamide

To a solution of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid (270 mg, 0.8 mmol) in anhydrous DMF (5 mL) was added NH_3 (6.4 mL, 0.5 *M* in 1,4-dioxane) and triethylamine (162 mg , 1.6 mmol). The resulting mixture was stirred for 10 mins, HATU (608 mg, 1.6 mmol) was added in batches and then the mixture was stirred overnight at room temperature. The mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL).The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzamide (20 mg).

Example 22: Preparation of (*R*)-2-[5-(3-chlorophenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (145 mg, 0.5 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (115 mg, 0.1 mmol), K_2CO_3 (138 mg, 1.0 mmol) and 3-chlorophenylboronic acid (94 mg, 0.6 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (50 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-chlorophenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (45 mg).

Example 23: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzonitrile

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-cyanophenylboronic acid (113 mg, 0.77 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was heated at 95 °C overnight, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzonitrile (25 mg).

Example 24: Preparation of (*R*)-2-[5-(4-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (100 mg, 0.342 mmol), 4-fluorophenylboronic acid (72 mg, 0.514 mmol), tetrakis(triphenylphosphine)palladium (20 mg, 0.017 mmol) and potassium carbonate (142 mg, 1.027 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (41 mg).

Example 25: Preparation of (*R*)-2-[5-(4-amino-3-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 4-bromo-2-fluoroaniline (40 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4 mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-amino-3-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (10 mg).

Example 26: Preparation of 3-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 3-hydroxyphenylboronic acid (106 mg, 0.77 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol (48 mg).

Example 27: Preparation of (*R*)-2-phenyl-2-[5-(1H-pyrazol-4-yl)-pyridin-3-ylamino]-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.514 mmol), 4-pyrazoleboronic acid pinacol ester (99 mg, 0.51 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol) and potassium carbonate (213 mg, 1.54 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-phenyl-2-[5-(1*H*-pyrazol-4-yl)-pyridin-3-ylamino]-ethanol (3.5 mg).

Example 28: Preparation of (*R*)-2-[5-(5-chloro-thiophen-2-yl)-pyridin-3-ylamino]-2-phenyl-ethanol

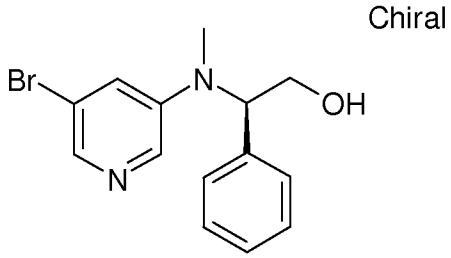
Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.51 mmol), 5-chlorothiophene-2-boronic acid (100 mg, 0.616 mmol), palladium acetate (12 mg, 0.05 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (42 mg, 0.103 mmol) and K_3PO_4 (218 mg, 1.027 mmol) in *n*-BuOH (5 mL) was heated at 100 °C overnight, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(5-chloro-thiophen-2-yl)-pyridin-3-ylamino]-2-phenyl-ethanol (4.6 mg).

Example 29: Preparation of 2-hydroxy-5-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-enzamide

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.6 mmol), 5-bromo-2-hydroxy-benzamide (125 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (33 mg) and potassium carbonate (160 mg, 1.2 mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-hydroxy-5-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-enzamide (3 mg).

Example 30: Preparation of (*R*)-2-{[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol

Step 1: Preparation of (*R*)-2-[(5-bromo-pyridin-3-yl)-methyl-amino]-2-phenyl-ethanol



A mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (3 g, 10.27 mmol), 38% aqueous formaldehyde (8.4 mL, 115.79 mmol), acetic acid (31.75 mL) in MeCN (30 mL) was stirred for 2 hours at room temperature. Then $NaBH_3CN$ (2.07 g, 32.88 mmol) was added slowly. After stirring overnight, water was added into the reaction mixture. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried, and then concentrated. The residue was

purified by flash column to give (*R*)-2-[(5-bromo-pyridin-3-yl)-methyl-amino]-2-phenyl-ethanol (300 mg).

Step 2: Preparation of (*R*)-2-{[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-[(5-bromo-pyridin-3-yl)-methyl-amino]-2-phenyl-ethanol (60 mg, 0.196 mmol), 5-chloro-2-fluorophenylboronic acid (68 mg, 0.392 mmol), tetrakis(triphenylphosphine)palladium (11 mg, 0.0098 mmol) and potassium carbonate (54 mg, 0.392 mmol) in DME/H_2O (5:1, 2 mL) was exposed to microwave irradiation at 100 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-{[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol (22 mg).

Example 31: Preparation of 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methoxy-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (200 mg, 0.68 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (342 mg, 1.37 mmol), tetrakis(triphenylphosphine)palladium (39.6 mg, 0.034 mmol) and potassium carbonate (283 mg, 2.05 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methoxy-phenol (98 mg).

Example 32: Preparation of 2-chloro-4-{5-[((*R*)-2-hydroxy-1-phenyl-ethyl)-methyl-amino]-pyridin-3-yl}-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-[(5-bromo-pyridin-3-yl)-methyl-amino]-2-phenyl-ethanol (60 mg, 0.196 mmol), 3-chloro-4-hydroxyphenylboronic acid, pinacol ester (50 mg, 0.196 mmol), tetrakis(triphenylphosphine)palladium (11 mg, 0.0098 mmol) and potassium carbonate (54 mg, 0.392 mmol) in DME/H_2O (5:1, 2 mL) was exposed to microwave irradiation at 100 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was

partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-chloro-4-{5-[((*R*)-2-hydroxy-1-phenyl-ethyl)-methyl-amino]-pyridin-3-yl}-phenol (15 mg).

Example 33: Preparation of (*R*)-2-{[5-(3-methoxy-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-[(5-bromo-pyridin-3-yl)-methyl-amino]-2-phenyl-ethanol (50 mg, 0.163 mmol), 3-methoxyphenylboronic acid (50 mg, 0.32 mmol), tetrakis(triphenylphosphine)palladium (9.4 mg, 0.008 mmol) and potassium carbonate (67 mg, 0.49 mmol) in DME/H_2O (5:1, 3 mL) was exposed to microwave irradiation at 95 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-{[5-(3-methoxy-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol (13 mg).

Example 34: Preparation of (*R*)-2-phenyl-2-[5-(3-trifluoromethoxy-phenyl)-pyridin-3-ylamino]-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 1-bromo-3-trifluoromethoxy-benzene (48 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4 mmol) in DME/H_2O (1:5, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-phenyl-2-[5-(3-trifluoromethoxy-phenyl)-pyridin-3-ylamino]-ethanol (11 mg).

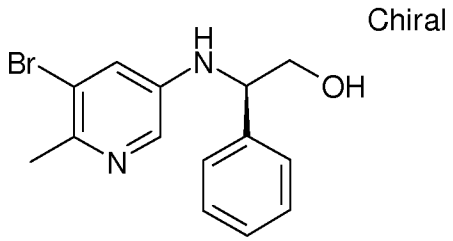
Example 35: Preparation of (*R*)-2-[5-(4-fluoro-3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-boronic acid-pyridin-3-ylamino)-2-phenyl-ethanol (50 mg, 0.2 mmol), 4-bromo-1-fluoro-2-methoxy-benzne (44 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (12 mg) and potassium carbonate (56 mg, 0.4 mmol) in DME/H_2O (1:5, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was

partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(4-fluoro-3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol (21 mg).

Example 36: Preparation of (*R*)-2-[5-(3-methoxy-phenyl)-6-methyl-pyridin-3-ylamino]-2-phenyl-ethanol

Step 1: Preparation of (*R*)-2-(5-bromo-6-methyl-pyridin-3-ylamino)-2-phenyl-ethanol



Under an Ar atmosphere, a mixture of 3,5-dibromo-2-methyl-pyridine (2 g, 8 mmol), D-(-)-alpha-phenylglycinol (1.32 g, 9.6 mmol), copper(I) iodide (0.15 g, 0.8 mmol), L-proline (0.184 g, 1.6 mmol) and potassium carbonate (2.2 g, 16 mmol) in DMSO (30 mL) was heated at 100 °C for 12 hours. The mixture was diluted with water and filtered to remove the catalyst. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, and then dried over Na_2SO_4 and concentrated. The residue was purified by chromatography column to give (*R*)-2-(5-bromo-6-methyl-pyridin-3-ylamino)-2-phenyl-ethanol (1 g).

Step 2: Preparation of (*R*)-2-[5-(3-methoxy-phenyl)-6-methyl-pyridin-3-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-6-methyl-pyridin-3-ylamino)-2-phenyl-ethanol (150 mg, 0.49 mmol), 3-methoxyphenylboronic acid (149 mg, 0.98 mmol), tetrakis(triphenylphosphine)palladium (28.3 mg, 0.0245 mmol) and potassium carbonate (203 mg, 1.47 mmol) in DME/H_2O (5:1, 3 mL) was exposed to microwave irradiation at 100 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(3-methoxy-phenyl)-6-methyl-pyridin-3-ylamino]-2-phenyl-ethanol (43 mg).

Example 37: Preparation of (*R*)-2-([3,3']bipyridinyl-5-ylamino)-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (300 mg, 1.027 mmol), 3-pyridylboronic acid (252 mg, 2.05 mmol), tetrakis(triphenylphosphine)palladium (59 mg, 0.05 mmol) and potassium carbonate (425 mg, 3.08 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 100 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-([3,3']bipyridinyl-5-ylamino)-2-phenyl-ethanol (100 mg).

Example 38: Preparation of (*R*)-2-(5'-fluoro-2'-methoxy-[3,4']bipyridinyl-5-ylamino)-2-phenyl-ethanol

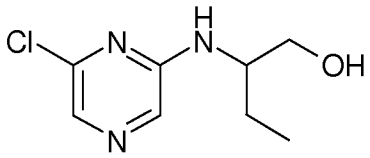
Under an Ar atmosphere, a mixture of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-phenyl-ethanol (300 mg, 1.027 mmol), (5-fluoro-2-methoxypyridin-4-yl)boronic acid (351 mg, 2.05 mmol), tetrakis(triphenylphosphine)palladium (59 mg, 0.051 mmol) and potassium carbonate (425 mg, 3.08 mmol) in DME/H_2O (5:1, 4.5 mL) was exposed to microwave irradiation at 100 °C for 1 hour, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-(5'-fluoro-2'-methoxy-[3,4']bipyridinyl-5-ylamino)-2-phenyl-ethanol (13 mg).

Example 39: Preparation of (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-(2-chloro-phenyl)-ethanol

To a solution of (*R*)-2-(5-bromo-pyridin-3-ylamino)-2-(2-chloro-phenyl)-ethanol (180 mg, 0.55 mmol) in DME/H_2O (5:1, 6 mL) was added $Pd(PPh_3)_4$ (127 mg, 0.1 mmol), K_2CO_3 (152 mg, 1.1 mmol) and 5-chloro-2-fluorophenylboronic acid (115 mg, 0.66 mmol). The resulting mixture was degassed and then stirred for 10 hours at 80 °C under an Ar atmosphere. After the reaction was completed as monitored by LC-MS, the mixture was cooled to room temperature, and then diluted with water (50 mL). The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[5-(5-chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-(2-chloro-phenyl)-ethanol (25 mg).

Example 40: Preparation of 2-(6-m-tolyl-pyrazin-2-ylamino)-butan-1-ol

Step 1: Preparation of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol



Under an Ar atmosphere, a mixture of 2,6-dichloropyrazine (1.2 g, 8 mmol) and 2-amino-butan-1-ol (1.43 g, 16 mmol) was exposed to microwave irradiation at 100 °C for 1 hour. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 1:1) to give 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (1.0 g) as yellow oil.

Step 2: Preparation of 2-(6-m-tolyl-pyrazin-2-ylamino)-butan-1-ol

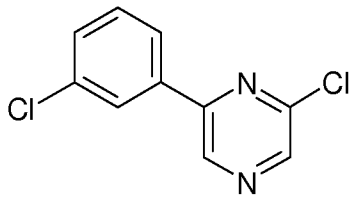
Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), *m*-tolylboronic acid (82 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (70 mg) and cesium carbonate (325 mg, 1mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-(6-m-tolyl-pyrazin-2-ylamino)-butan-1-ol (88 mg).

Example 41: Preparation of 4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol

To a solution of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (250 mg, 1.25 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (288 mg, 0.25 mmol), K_2CO_3 (345 mg, 2.5 mmol) and 4-hydroxyphenylboronic acid (207 mg, 1.5 mmol). The resulting mixture was degassed and then stirred overnight at 90 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give 4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol (20 mg).

Example 42: Preparation of (*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-3-phenyl-propan-1-ol

Step 1: Preparation of 2-chloro-6-(3-chloro-phenyl)-pyrazine



To a solution of 2,6-dichloropyrazine (6.0 g, 40 mmol) in DMF/H_2O (5:1, 55 mL) was added $Pd_2(PPh_3)_2Cl_2$ (5.6 g, 8 mmol), Na_2CO_3 (8.5 g, 80 mmol) and 3-chlorophenylboronic acid (7.5 g, 48 mmol). The resulting mixture was degassed and then stirred overnight at 80 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 3:1) to give 2-chloro-6-(3-chloro-phenyl)-pyrazine (6 g) as a white solid.

Step 2: Preparation of (*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-3-phenyl-propan-1-ol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (225 mg, 1.0 mmol) and (*R*)-2-amino-3-phenyl-propan-1-ol (300 mg, 2.0 mmol) was exposed to microwave irradiation at 180 °C for 1 hour. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(3-chlorophenyl)-pyrazin-2-ylamino]-3-phenyl-propan-1-ol (50 mg).

Example 43: Preparation of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 3-aminocarbonylphenylboronic acid (100 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (70 mg) and cesium carbonate (325 mg, 1 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide (4 mg).

Example 44: Preparation of 2-[6-(4-methanesulfonyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 4-(methanesulfonyl)phenylboronic acid (120 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (70 mg) and cesium carbonate (325 mg, 1 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(4-methanesulfonyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol (35 mg).

Example 45: Preparation of 5-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-pyridin-2-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol (132 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (70 mg) and cesium carbonate (325 mg, 1 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 5-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-pyridin-2-ol (18 mg).

Example 46: Preparation of 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 5-chloro-2-fluorophenylboronic acid (104mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (25 mg) and cesium carbonate (325 mg, 1 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic extracts were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (18 mg).

Example 47: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(4-fluoro-phenyl)-ethanol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (112.5 mg,

0.5 mmol) and 2-amino-2-(4-fluoro-phenyl)-ethanol (230 mg, 1.5 mmol) was exposed to microwave irradiation at 180 °C for 1 hour. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(4-fluoro-phenyl)-ethanol (10 mg).

Example 48: Preparation of 2-[6-(6-amino-pyridin-3-yl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 2-aminopyridine-5-boronic acid, pinacol ester (110 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)- biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(6-amino-pyridin-3-yl)-pyrazin-2-ylamino]-butan-1-ol (80 mg).

Example 49: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (225 mg, 1.0 mmol) and 2-amino-2-methyl-propan-1-ol (286 mg, 3.0 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol (30 mg).

Example 50: Preparation of {1-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (225 mg, 1.0 mmol) and (1-amino-cyclopentyl)-methanol (345 mg, 3.0 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS,

the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give {1-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol (8 mg).

Example 51: Preparation of 2-[6-(2-fluoro-5-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 5-methyl-2-fluorophenylboronic acid (90 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)- biphenyl (10mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(2-fluoro-5-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol (43 mg).

Example 52: Preparation of 2-[6-(3-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 3-chloro-2-fluorophenylboronic acid (90 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)- biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (13 mg).

Example 53: Preparation of 2-[6-(2, 5-dichloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 2,5-dichlorophenylboronic acid (100 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)- biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was

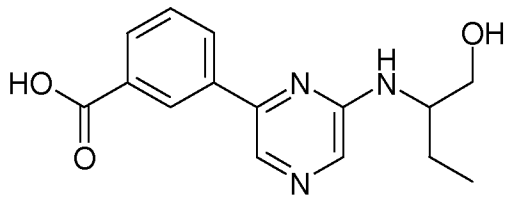
heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(2, 5-dichloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (12 mg).

Example 54: Preparation of 2-[6-(3-chloro-5-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 3-fluoro-5-chlorophenylboronic acid (90 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-5-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (13 mg).

Example 55: Preparation of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-N-methyl-benzamide

Step 1: Preparation of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzoic acid



Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 3-carboxyphenylboronic acid (85 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzoic acid (114 mg).

Step 2: Preparation of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-*N*-methyl-benzamide

A mixture of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzoic acid (72 mg, 0.25 mmol), methylamine solution in THF (0.28 mL, 1M), *N*-hydroxybenzotrizole (34 mg, 0.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg 0.5 mmol) and 4-methylmorpholine (50 mg, 0.5 mmol) in DMF was stirred at room temperature for 3 hours. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-*N*-methyl-benzamide (23 mg).

Example 56: Preparation of 2-[6-(4-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 4-fluoro-phenylboronic acid (85 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(4-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (39 mg).

Example 57: Preparation of *N*-(2-hydroxy-ethyl)-3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide

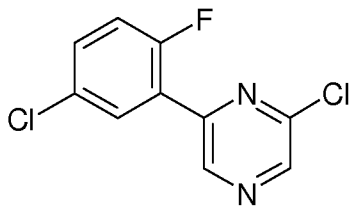
A mixture of 3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzoic acid (72 mg, 0.25 mmol), 2-amino-ethanol (20 mg, 0.28 mmol), *N*-hydroxybenzotrizole (34 mg, 0.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg 0.5 mmol) and 4-methylmorpholine (50 mg, 0.5 mmol) in DMF was stirred at room temperature for 3 hours. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give *N*-(2-hydroxy-ethyl)-3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide (12 mg).

Example 58: Preparation of 1-{[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-methyl}-cyclohexanol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (225 mg, 1.0 mmol) and 1-aminomethyl-cyclohexanol (447 mg, 3.0 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After cooling, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 1-{[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-methyl}-cyclohexanol (18 mg).

Example 59: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-3-methyl-butan-1-ol

Step 1: Preparation of 2-chloro-6-(5-chloro-2-fluorophenyl)-pyrazine



To a solution of 2, 6-dichloropyrazine (3.0 g, 20 mmol) in DMF/H_2O (5:1, 30 mL) was added $Pd_2(PPh_3)_2Cl_2$ (2.8 g, 4 mmol), Na_2CO_3 (4.25 g, 40 mmol) and 5-chloro-2-fluorophenylboronic acid (4.2 g, 24 mmol). The resulting mixture was degassed and then stirred overnight at 80 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (100 mL) and then extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 3:1) to give 2-chloro-6-(5-chloro-2-fluoro-phenyl)-pyrazine (1.6 g) as a white solid.

Step 2: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-3-methyl-butan-1-ol

Under an Ar atmosphere, a mixture of 2-chloro-6-(5-chloro-2-fluorophenyl)-pyrazine (120 mg, 0.5 mmol) and (*R*)-2-amino-3-methyl-butan-1-ol (154 mg, 1.5 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-3-methyl-butan-1-ol (35 mg).

Example 60: Preparation of 2-[6-(5-chloro-2-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol

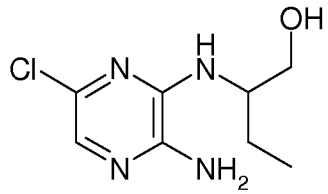
Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 5-chloro-2-methylbenzeneboronic acid (102 mg, 0.6 mmol), tetrakis(triphenylphosphine)palladium (25 mg) and potassium carbonate (280 mg, 1 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(5-chloro-2-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol (5 mg).

Example 61: Preparation of 2-[6-(3-ethyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 3-ethyl-benzeneboronic acid (75 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-ethyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol (70 mg).

Example 62: Preparation of 2-[3-amino-6-(3-chloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Step 1: Preparation of 2-(3-amino-6-chloro-pyrazin-2-ylamino)-butan-1-ol



Neat reaction between 3, 5-dichloro-pyrazin-2-ylamine (1 g, 4.6 mmol) and 2-amino-butan-1-ol (1.23 g, 13.8 mmol) was carried out under microwave at 120 °C for 1 hour. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was

purified by column chromatography to give 600 mg of 2-(3-amino-6-chloro-pyrazin-2-ylamino)-butan-1-ol.

Step 2: Preparation of 2-[3-amino-6-(3-chloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(3-amino-6-chloro-pyrazin-2-ylamino)-butan-1-ol (110 mg, 0.5 mmol), 3-chloro-benzeneboronic acid (94 mg, 0.6 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)- biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[3-amino-6-(3-chloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol (3 mg).

Example 63: Preparation of 2-chloro-6-(5-chloro-2-fluorophenyl)-pyrazine

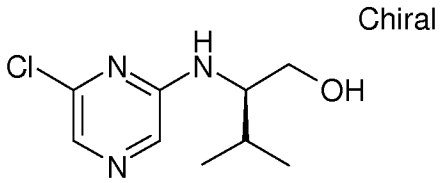
Under an Ar atmosphere, a mixture of 2-chloro-6-(5-chloro-2-fluorophenyl)-pyrazine (120 mg, 0.5 mmol) and 2-amino-pentan-1-ol (154 mg, 1.5 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-pentan-1-ol (5 mg).

Example 64: Preparation of {1-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol

Under an Ar atmosphere, a mixture of 2-chloro-6-(5-chloro-2-fluoro-phenyl)-pyrazine (120 mg, 0.5 mmol) and (1-amino-cyclopentyl)-methanol (170 mg, 1.5 mmol) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give {1-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol (5 mg).

Example 65: Preparation of 4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol

Step 1: Preparation of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-3-methyl-butan-1-ol



Under an Ar atmosphere, a mixture of 2,6-dichloropyrazine (1.8 g, 12 mmol) and (*R*)-2-amino-3-methyl-butan-1-ol (2.5 g, 24 mmol) was exposed to microwave irradiation at 160 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 1:1) to give (*R*)-2-(6-chloro-pyrazin-2-ylamino)-3-methyl-butan-1-ol (1.15 g) as a yellow solid.

Step 2: Preparation of 4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol

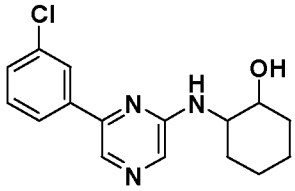
To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-3-methyl-butan-1-ol (215 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 4-hydroxyphenylboronic acid (165.6 mg, 1.2 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give 4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol (20 mg).

Example 66: Preparation of 3-fluoro-4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol

Under an Ar atmosphere, a mixture of 2-(3-amino-6-chloro-pyrazin-2-ylamino)-butan-1-ol (110 mg, 0.5 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (120 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-fluoro-4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol (32 mg).

Example 67: Preparation of (1*S*, 2*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol

Step 1: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol



Neat reaction between 2-chloro-6-(4-chloro-phenyl)-pyrazine (100 mg, 0.44 mmol) and 2-amino-cyclohexanol (350 mg, 1.32 mmol) was carried out under microwave at 180 °C for 30 mins. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography to give 200 mg of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol.

Step 2: Preparation of (1*S*, 2*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol

Chiral separation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol gave (1*S*, 2*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol (3 mg).

Example 68: Preparation of (1*R*, 2*S*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol

Chiral separation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol gave (1*R*, 2*S*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol (4 mg).

Example 69: Preparation of (1*R*, 2*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol

Chiral separation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol gave (1*R*, 2*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol (21 mg).

Example 70: Preparation of (1*S*, 2*S*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol

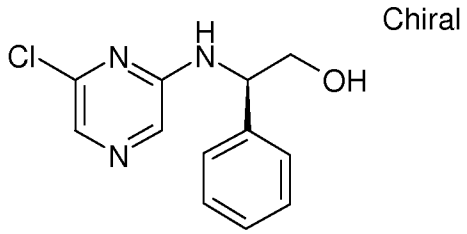
Chiral separation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol gave (1*S*, 2*S*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol (26 mg).

Example 71: Preparation of 2-[6-(5-chloro-thiophen-2-yl)-pyrazin-2-ylamino]-butan-1-ol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-butan-1-ol (100 mg, 0.5 mmol), 5-chlorothiophene-2-boronic acid (81 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(5-chloro-thiophen-2-yl)-pyrazin-2-ylamino]-butan-1-ol (10 mg).

Example 72: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol

Step 1: Preparation of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol



Under an Ar atmosphere, a mixture of 2,6-dichloropyrazine (1.5 g, 10 mmol) and (*R*)-2-amino-2-phenyl-ethanol (4.1 g, 30 mmol) in isopropanol (10 mL) was exposed to microwave irradiation at 180 °C for 1.5 hours. After the reaction was completed as monitored by LC-MS, the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography (EtOAc / PE = 2:1) to give (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (850 mg) as a light yellow solid.

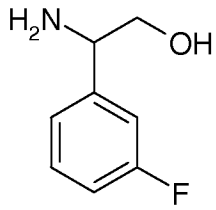
Step 2: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (250 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 5-chloro-2-fluorophenylboronic acid (260 mg, 1.5 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture

was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol (30 mg).

Example 73: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-fluoro-phenyl)-ethanol

Step 1: Preparation of 2-amino-2-(3-fluoro-phenyl)-ethanol



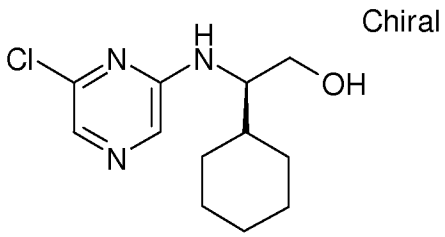
Amino-(3-fluoro-phenyl)-acetic acid (1.8 g, 10 mmol), $NaBH_4$ (0.95 g, 2.5 mmol) and THF (30 mL) were added dropwise to a solution of iodine (2.54 g, 10 mmol) in anhydrous THF (7 mL) through a pressure-equalizing addition funnel at 0 °C. After the ceasing of the hydrogen gas, the reaction mixture was heated to reflux for 20 hours and then cooled to room temperature. The reaction was quenched with methanol, and then dissolved in 20% aqueous KOH. The reaction mixture was stirred overnight to give 1.4 g of crude 2-amino-2-(3-fluoro-phenyl)-ethanol which was directly used in the next step.

Step 2: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-fluoro-phenyl)-ethanol

Neat reaction between 2-chloro-6-(4-chloro-phenyl)-pyrazine (100 mg, 0.44 mmol) and 2-amino-2-(3-fluoro-phenyl)-ethanol (205 mg, 1.32 mmol) was carried out under microwave at 180 °C for 30 mins. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-fluoro-phenyl)-ethanol (8 mg).

Example 74: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-cyclohexyl-ethanol

Step 1: Preparation of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-cyclohexyl-ethanol



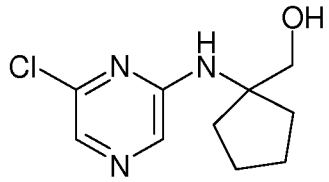
Under an Ar atmosphere, a mixture of 2,6-dichloro-pyrazine (149 mg, 1.0 mmol), (*R*)-2-amino-2-cyclohexyl-ethanol (171 mg, 1.2 mmol), 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (4 mg), palladium (II) acetate (2 mg) and lithium bis(trimethylsilyl)amide (2 mL, 1M) in THF (10 mL) was heated at 100 °C overnight. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography to give (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-cyclohexyl-ethanol (60 mg).

Step 2: Preparation of (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-cyclohexyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-cyclohexyl-ethanol (40 mg, 0.16 mmol), 5-chloro-2-fluorobenzeneboronic acid (30 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium (10 mg) and potassium carbonate (44 mg, 0.32 mmol) in DME/H_2O (5:1, 5 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-cyclohexyl-ethanol (3 mg).

Example 75: Preparation of 3-fluoro-4-[6-(1-hydroxymethyl-cyclopentylamino)-pyrazin-2-yl]-phenol

Step 1: Preparation of [1-(6-chloro-pyrazin-2-ylamino)-cyclopentyl]-methanol



Neat reaction between 2, 6-dichloro-pyrazine (150 g, 1 mmol) and (1-amino-cyclopentyl)-methanol (345 mg, 3 mmol) was carried out under microwave at 120 °C for 1 hour. Then the

mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography to give 120 mg of [1-(6-chloro-pyrazin-2-ylamino)-cyclopentyl]-methanol.

Step 2: Preparation of 3-fluoro-4-[6-(1-hydroxymethyl-cyclopentylamino)-pyrazin-2-yl]-phenol

Under an Ar atmosphere, a mixture of [1-(6-chloro-pyrazin-2-ylamino)-cyclopentyl]-methanol (60 mg, 0.5 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (60 mg, 0.5 mmol), bis(triphenylphosphine)palladium(II) chloride (7 mg), 2-(dicyclohexylphosphino)-biphenyl (10 mg) and sodium carbonate (106 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 3-fluoro-4-[6-(1-hydroxymethyl-cyclopentylamino)-pyrazin-2-yl]-phenol (9 mg).

Example 76: Preparation of (*R*)-2-[6-(4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (250 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 4-hydroxyphenylboronic acid (207 mg, 1.5 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol (5 mg).

Example 77: Preparation of (*R*)-2-[6-(2-fluoro-4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (250 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 2-fluoro-4-hydroxyphenylboronic acid (234 mg, 1.5 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the

mixture was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(2-fluoro-4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol (15 mg).

Example 78: Preparation of 3-fluoro-4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol

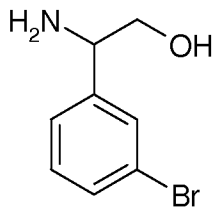
To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-3-methyl-butan-1-ol (215 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 2-fluoro-4-hydroxyphenylboronic acid (187 mg, 1.2 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give 3-fluoro-4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol (8 mg).

Example 79: Preparation of 4-[6-((*R*)-1-cyclohexyl-2-hydroxy-ethylamino)-pyrazin-2-yl]-3-fluoro-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-cyclohexyl-ethanol (62 mg, 0.2 mmol), 3-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (50 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) chloride (5 mg), 2-(dicyclohexylphosphino)-biphenyl (8 mg) and sodium carbonate (50 mg, 1 mmol) in 1,4-dioxane/EtOH /H_2O (1:1:1, 6 mL) was heated at 130 °C under microwave for 15 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 4-[6-((*R*)-1-cyclohexyl-2-hydroxy-ethylamino)-pyrazin-2-yl]-3-fluoro-phenol (2 mg).

Example 80: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-bromo-phenyl)-ethanol

Step 1: Preparation of 2-amino-2-(3-bromo-phenyl)-ethanol



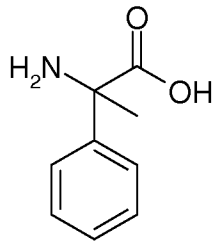
Amino-(3-bromo-phenyl)-acetic acid (2.3 g 10 mmol), $NaBH_4$ (0.95 g, 2.5 mmol) and THF (30 mL) were added dropwise into a solution of iodine (2.54 g, 10 mmol) in anhydrous THF (7 mL) through a pressure-equalizing addition funnel at 0 °C. After the ceasing of the hydrogen gas, the reaction mixture was heated to reflux for 20 hours and then cooled to room temperature. The reaction was quenched with methanol, and then dissolved in 20% aqueous KOH. and the reaction mixture was stirred overnight to give 2 g of crude 2-amino-2-(3-bromo-phenyl)-ethanol which was directly used in the next step.

Step 2: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-bromo-phenyl)-ethanol

Neat reaction between 2-chloro-6-(4-chloro-phenyl)-pyrazine (100 mg, 0.44 mmol) and 2-amino-2-(3-bromo-phenyl)-ethanol (205 mg, 1.32 mmol) was carried out under microwave at 180 °C for 30 mins. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-(3-bromo-phenyl)-ethanol (3 mg).

Example 81: Preparation of 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-propan-1-ol

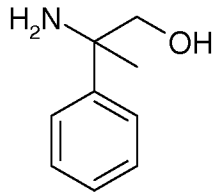
Step 1: Preparation of 2-amino-2-phenyl-propionic acid



A 250 mL round bottomed flask equipped with magnetic stirring bar was added 1-phenyl-ethanone (18 g, 150 mmol), NH_4Cl (9.2 g, 172 mmol), ammonia (20 ml, 270 mmol), ethanol (45 mL) and water (38 mL). After the mixture was dissolved, NaCN (8.5 g, 173 mmol) was added, and then the flask was quickly sealed with a rubber stopper. The mixture was stirred for 8 hours at 65 °C. The reaction mixture was cooled to room temperature, and then extracted with DCM (3

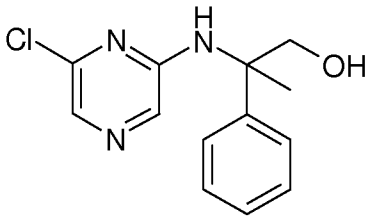
× 30 mL). The organic layer was washed with water to remove the remaining NaCN, and then dried over anhydrous sodium sulfate. The solvent is concentrated under pressure to afford crude amino nitrile which was used directly in the next step. Then the flask containing the previously mentioned crude amino nitrile was equipped with magnetic stirring bar and condenser, cooled in an ice water bath. Hydrochloride acid (150 mL) which was precooled in an ice water bath was poured into the flask. The resulting mixture was stirred overnight, and then diluted with water (150 mL). The reaction mixture was heated at reflux for 3 hours. The azeotrope of remaining ketone, HCl and water was distilled off. The aqueous layer was extracted with DCM (3 × 50 mL). The aqueous solution was evaporated *in vacuo* to give 2-amino-2-phenyl-propionic acid (13.8 g).

Step 2: Preparation of 2-amino-2-phenyl-propan-1-ol



2-Amino-2-phenyl-propionic acid (3.3 g 20 mmol), $NaBH_4$ (1.9 g, 50 mmol) and THF 30 mL were added dropwise to a solution of iodine (5.08 g, 20 mmol) in anhydrous THF (20 mL) through a pressure-equalizing addition funnel at 0 °C. After the ceasing of the hydrogen gas, the reaction mixture was heated to reflux for 20 hours and then cooled to room temperature. The reaction was quenched with methanol, and then dissolved in 20% aqueous KOH. The reaction mixture was stirred overnight to give crude 2-amino-2-phenyl-propan-1-ol (3 g).

Step 3: Preparation of 2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-propan-1-ol



Neat reaction between 3,5-dichloro-pyrazin-2-ylamine (1 g, 4.6 mmol) and 2-amino-2-phenyl-propan-1-ol (2.1 g, 13.8 mmol) was carried out under microwave at 120 °C for 1 hour. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography to give pure 2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-propan-1-ol (600 mg).

Step 4: Preparation of 2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-propan-1-ol

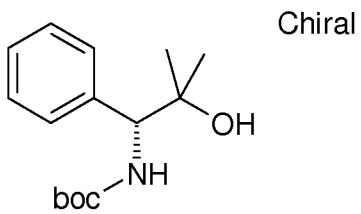
Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-propan-1-ol (53 mg, 0.2 mmol), 3-chlorobenzeneboronic acid (32 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (10 mg) and potassium carbonate (55 mg, 0.5 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the reaction mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-propan-1-ol (12 mg).

Example 82: Preparation of 2-chloro-4-[6-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyrazin-2-yl]-phenol

Under an Ar atmosphere, a mixture of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (102 mg, 0.4 mmol), 2-chloro-4-(4, 4, 5, 5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol (100 mg, 0.4 mmol), tetrakis(triphenylphosphine)palladium (23 mg) and potassium carbonate (110 mg, 0.8 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the reaction mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-chloro-4-[6-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyrazin-2-yl]-phenol (70 mg).

Example 83: Preparation of (*R*)-1-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-methyl-1-phenyl-propan-2-ol

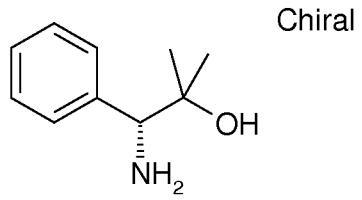
Step 1: Preparation of ((*R*)-2-hydroxy-2-methyl-1-phenyl-propyl)-carbamic acid tert-butyl ester



(*R*)-*tert*-butoxycarbonylamino-phenyl-acetic acid methyl ester (5.32 g, 20 mmol) was dissolved in 80 mL of THF. After cooling to 0 °C, 3M MeMgBr solution in THF (22 mL, 64 mmol) was added into the reaction mixture dropwise. The reaction was stirred at 0 °C for 1 hour

and then was warmed to room temperature. The reaction mixture was stirred for another 3 hours. The reaction was quenched with saturated NH_4Cl, and then extracted with DCM. The combined organic layers were dried and concentrated to give crude product ((*R*)-2-hydroxy-2-methyl-1-phenyl-propyl)-carbamic acid *tert*-butyl ester (5.5 g).

Step 2: Preparation of (*R*)-1-amino-2-methyl-1-phenyl-propan-2-ol



The crude ((*R*)-2-hydroxy-2-methyl-1-phenyl-propyl)-carbamic acid *tert*-butyl ester (5.5 g, 20.8 mmol) was dissolved in 15 mL of 1,4-dioxane, then 20 mL of 4 M HCl/dioxane solution was added. The mixture was stirred at room temperature for 2 hours. The reaction was quenched with saturated Na_2CO_3 aqueous solution, and then EtOAc was added. The combined organic layers were concentrated to get crude product (*R*)-1-amino-2-methyl-1-phenyl-propan-2-ol (2.6 g).

Step 3: Preparation of (*R*)-1-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-methyl-1-phenyl-propan-2-ol

Neat reaction between 2-chloro-6-(5-chloro-2-fluoro-phenyl)-pyrazine (500 mg, 2.07 mmol) and (*R*)-1-amino-2-methyl-1-phenyl-propan-2-ol (1.02 g, 6.21 mmol) was carried out under microwave at 180 °C for 1 hour. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give pure (*R*)-1-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-methyl-1-phenyl-propan-2-ol (6 mg).

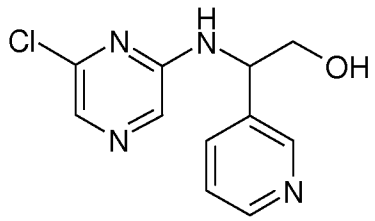
Example 84: Preparation of (*R*)-2-[6-(5-chloro-pyridin-3-yl)-pyrazin-2-ylamino]-2-phenyl-ethanol

Under an Ar atmosphere, a mixture of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (80 mg, 0.32 mmol), 5-chloropyridine-3-boronic acid (50 mg, 0.32 mmol), tetrakis(triphenylphosphine)palladium (18 mg) and potassium carbonate (88 mg, 0.64 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by

Prep-HPLC to give (*R*)-2-[6-(5-chloro-pyridin-3-yl)-pyrazin-2-ylamino]-2-phenyl-ethanol (9 mg).

Example 85: Preparation of 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-pyridin-3-yl-ethanol

Step 1: Preparation of 2-(6-chloro-pyrazin-2-ylamino)-2-pyridin-3-yl-ethanol



Neat reaction between 3, 5-dichloro-pyrazin-2-ylamine (150 mg, 1 mmol) and 2-amino-2-pyridin-3-yl-ethanol (420 mg, 3 mmol) was carried out under microwave at 120 °C for 1 hour. Then the mixture was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by column chromatography to give pure 2-(6-chloro-pyrazin-2-ylamino)-2-pyridin-3-yl-ethanol (100 mg).

Step 2: Preparation of 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-pyridin-3-yl-ethanol

Under an Ar atmosphere, a mixture of 2-(6-chloro-pyrazin-2-ylamino)-2-pyridin-3-yl-ethanol (50 mg, 0.2 mmol), 2-fluoro-5-chlorobenzeneboronic acid (35 mg, 0.2 mmol), tetrakis(triphenylphosphine)palladium (23 mg) and potassium carbonate (55 mg, 0.5 mmol) in DME/H_2O (5:1, 8 mL) was heated at 90 °C under microwave for 40 mins. Then the residue was partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give 2-[6-(5-chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-pyridin-3-yl-ethanol (22 mg).

Example 86: Preparation of (*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol

To a solution of (*R*)-2-(6-chloro-pyrazin-2-ylamino)-2-phenyl-ethanol (250 mg, 1.0 mmol) in DME/H_2O (5:1, 18 mL) was added $Pd(PPh_3)_4$ (230 mg, 0.2 mmol), K_2CO_3 (276 mg, 2.0 mmol) and 3-chlorophenylboronic acid (234 mg, 1.5 mmol). The resulting mixture was degassed and then stirred overnight at 85 °C under an Ar atmosphere. After cooling, the mixture was

diluted with water (75 mL) and then extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine, and then dried. The solvent was concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol (26 mg).

Example 87: Preparation of (*R*)-2-[6-(3-chloro-phenyl)-pyrazin-2-ylamino]-4-methyl-pentan-1-ol

Under an Ar atmosphere, a mixture of 2-chloro-6-(3-chloro-phenyl)-pyrazine (225 mg, 1.0 mmol) and (*R*)-2-amino-4-methyl-pentan-1-ol (235 mg, 2.0 mmol) was exposed to microwave irradiation at 180 °C for 1 hour. After the reaction was completed as monitored by LC-MS, the reaction mixture was cooled to room temperature, and then partitioned between EtOAc and brine. The aqueous layer was separated and then extracted with EtOAc. The combined organic layers were concentrated, and then the residue was purified by Prep-HPLC to give (*R*)-2-[6-(3-chlorophenyl)-pyrazin-2-ylamino]-4-methyl-pentan-1-ol (45 mg).

BIOLOGICAL EXAMPLES

Example 88: CDK8/Cyclin C LANCE TR-FRET kinase assay:

The biological activity of the compounds of the invention can be determined using the assay described below.

CDK8/Cyclin C protein was obtained from Invitrogen, cat# PV4402. U*Light*-Glycogen Synthase (Ulight-GS) peptide with sequence PASVPPSPSLSRHSSPHQ(pS)ED, and Europium-anti-phospho Glycogen Synthase (Ser641) [Eu-anti-P-GS (Ser641)] were obtained from Perkin Elmer, cat# TRF0131-M and cat# TRF0220. Adenosine-5'-triphosphate (ATP) was obtained from Invitrogen, cat# PV3227.

A mixture of (1) a compound of formula I, (2) substrate [Ulight-GS peptide (80 nM) and ATP (24 μM)], and (3) CDK8/Cyclin C (10 nM) in reaction buffer (50 mM Hepes, pH7.0, 10 mM $MgCl_2$, 1 mM EGTA, 0.2 mg/mL BSA, 0.8 mM DTT) were incubated at 37 °C for 30 mins. Then, [Eu-anti-P-GS (Ser641)] (1.5 nM) was added. Following incubation at room temperature for 30 mins, the TR-FRET signals were detected using Envision reader (Ex 340 nm, Em 615 nm and 665 nm) from Perkin Elmer. The reactivity in percentage of inhibition or dose response was analyzed with GraphPad Prism 5 (GraphPad Software).

Results of CDK8/Cyclin LANCE Ultra biochemical TR-FRET kinase assay are given in Table 1.

Example 89: ***In vitro*** **cell proliferation assay:**

Cells were seeded on 96-well plates at 5×10^3 cells per well and precultured for 24 hours. The cells were treated with serial diluted compounds and cultured for 72 hours. Then all media was discarded and after that, 100 µL 1:10 (v/v) Cell Counting Kit-8 (CCK-8)-culture media solution was added to the wells. Plate was developed for 2 hours in an incubator, and the absorbance was measured at 450 nm wavelengths with SpectraMAX190 (MDS, Sunnyvale, CA). The inhibition rate (IR) of the tested compounds was determined with following formula: IR (%)= $(OD_{DMSO}$-ODcompound)/$OD_{DMSO} \times 100\%$. The concentration corresponding to 50% IR (IC_{50}) was determined with plot curve of IR against tested compound concentrations with SoftMax Pro.

Results of *in vitro* cell proliferation assay are given in Table 3.

The compounds of the present invention were tested for their capacity to inhibit a CDK8 activity and activation as described herein. The Examples were tested in the above assay and found to have IC_{50} of about 0.0001 µM to about 30 µM. Particular compounds of formula I were found to have IC_{50} of about 0.0001 µM to about 1 µM.

Example A

A compound of formula I can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

	Per tablet
Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

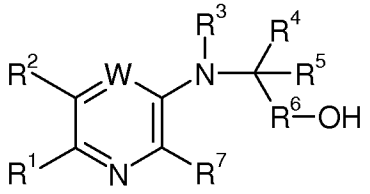
Example B

A compound of formula I can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

Claims

1. Compounds of formula (I)



(I)

wherein

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is phenyl, pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice or three times substituted by amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylsulfonyl, carboxy, cyano, halogen, hydroxy, hydroxy-C_xH_{2x}-, hydroxy-C_yH_{2y}-aminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl, cycloalkyl, phenyl, halophenyl, phenyl-C_xH_{2x}- or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cycloalkyl;

R^6 is -C_xH_{2x}- or cycloalkyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cycloalkyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

x is 1-6;

y is 2-6;

or pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

R^1 is hydrogen or methyl;

R^2 is phenyl, pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice or three times substituted by amino, aminocarbonyl, methoxy, methyl, ethyl, methylaminocarbonyl, methylsulfonyl, carboxy, cyano, fluoro, chloro, hydroxy, hydroxymethyl, hydroxyethylaminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclohexyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, phenylmethyl or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cyclopentyl;

R^6 is $-CH_2-$, $-C(CH_3)_2$ or cyclohexyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cyclohexyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

or pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein

R^1 is hydrogen;

R^2 is pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice substituted by amino, C_{1-6}alkoxy, halogen or hydroxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is C_{1-6}alkyl or phenyl;

R^6 is $-C_xH_{2x}-$;

R^7 is hydrogen;

W is -N- or -CH;

x is 1-6.

4. A compound according to claim 3, wherein

R^1 is hydrogen;

R^2 is pyrazolyl, pyridinyl or thienyl; which is unsubstituted or once or twice substituted by amino, methoxy, fluoro, chloro or hydroxy;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is ethyl or phenyl;

R^6 is $-CH_2-$;

R^7 is hydrogen;

W is -N- or -CH.

5. A compound according to claim 1, wherein

R^1 is hydrogen or C_{1-6}alkyl;

R^2 is phenyl; which is once or twice or three times substituted by amino, aminocarbonyl, C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkylsulfonyl, carboxy, cyano, halogen, hydroxy, hydroxy-C_xH_{2x}-, hydroxy-C_yH_{2y}-aminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen, C_{1-6}alkyl, cycloalkyl, phenyl, halophenyl, phenyl-C_xH_{2x}- or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cycloalkyl;

R^6 is -C_xH_{2x}- or cycloalkyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cycloalkyl;

R^7 is hydrogen or amino;

W is -N- or -CH;

x is 1-6;

y is 2-6.

6. A compound according to claim 5, wherein

R^1 is hydrogen or methyl;

R^2 is phenyl; which is once or twice or three times substituted by amino, aminocarbonyl, methoxy, methyl, ethyl, methylaminocarbonyl, methylsulfonyl, carboxy, cyano, fluoro, chloro, hydroxy, hydroxymethyl, hydroxyethylaminocarbonyl or trifluoromethyl-O-;

R^3 is hydrogen or methyl;

R^4 is hydrogen or methyl;

R^5 is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, cyclohexyl, phenyl, fluorophenyl, chlorophenyl, bromophenyl, phenylmethyl or pyridinyl;

or R^4 and R^5, together with the carbon atom, to which they are attached, form cyclopentyl;

R^6 is -CH_2-, -$C(CH_3)_2$ or cyclohexyl;

or R^5 and R^6, together with the carbon atom, to which they are attached, form cyclohexyl;

R^7 is hydrogen or amino;

W is -N- or -CH.

7. A compound according to any one of claims 1 to 6, selected from

2-[5-(3-Chloro-phenyl)-pyridin-3-ylamino]-butan-1-ol;

(*R*)-2-[5-(3-chloro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol;

(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol;
(*R*)-2-[5-(4-Hydroxy-2-fluoro-phenyl)-pyridin-3-ylamino]-3-methyl-butan-1-ol;
{1-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-cyclopentyl}-methanol;
(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(2-Fluoro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(3-Chloro-4-hydroxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methyl-phenol;
2-Fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;
2-Chloro-5-fluoro-4-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;
(*R*)-2-[5-(3-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(4-Chloro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-Phenyl-2-(5-p-tolyl-pyridin-3-ylamino)-ethanol;
(*R*)-2-[5-(4-Methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(4-Hydroxymethyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(3-Amino-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
2-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;
(*R*)-2-[5-(4-Methoxy-2-methyl-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzoic acid;
4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzamide;
(*R*)-2-[5-(3-Chlorophenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-benzonitrile;
(*R*)-2-[5-(4-Fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
(*R*)-2-[5-(4-Amino-3-fluoro-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;
3-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-phenol;
(*R*)-2-Phenyl-2-[5-(1H-pyrazol-4-yl)-pyridin-3-ylamino]-ethanol;
(*R*)-2-[5-(5-Chloro-thiophen-2-yl)-pyridin-3-ylamino]-2-phenyl-ethanol;
2-Hydroxy-5-[5-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-enzamide;
(*R*)-2-{[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol;
4-[5-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-pyridin-3-yl]-2-methoxy-phenol;
2-Chloro-4-{5-[((*R*)-2-hydroxy-1-phenyl-ethyl)-methyl-amino]-pyridin-3-yl}-phenol;
(*R*)-2-{[5-(3-Methoxy-phenyl)-pyridin-3-yl]-methyl-amino}-2-phenyl-ethanol;
(*R*)-2-Phenyl-2-[5-(3-trifluoromethoxy-phenyl)-pyridin-3-ylamino]-ethanol;
(*R*)-2-[5-(4-Fluoro-3-methoxy-phenyl)-pyridin-3-ylamino]-2-phenyl-ethanol;

(*R*)-2-[5-(3-Methoxy-phenyl)-6-methyl-pyridin-3-ylamino]-2-phenyl-ethanol;

(*R*)-2-([3,3']Bipyridinyl-5-ylamino)-2-phenyl-ethanol;

(*R*)-2-(5'-Fluoro-2'-methoxy-[3,4']bipyridinyl-5-ylamino)-2-phenyl-ethanol;

(*R*)-2-[5-(5-Chloro-2-fluoro-phenyl)-pyridin-3-ylamino]-2-(2-chloro-phenyl)-ethanol;

2-(6-*m*-Tolyl-pyrazin-2-ylamino)-butan-1-ol;

4-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol;

(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-3-phenyl-propan-1-ol;

3-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide;

2-[6-(4-Methanesulfonyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

5-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-pyridin-2-ol;

2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(4-fluoro-phenyl)-ethanol;

2-[6-(6-Amino-pyridin-3-yl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol;

{1-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol;

2-[6-(2-Fluoro-5-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(3-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(2,5-Dichloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(3-Chloro-5-fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

3-[6-(1-Hydroxymethyl-propylamino)-pyrazin-2-yl]-*N*-methyl-benzamide;

2-[6-(4-Fluoro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

N-(2-Hydroxy-ethyl)-3-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-benzamide;

1-{[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-methyl}-cyclohexanol;

(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-3-methyl-butan-1-ol;

2-[6-(5-Chloro-2-methyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[6-(3-Ethyl-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-[3-Amino-6-(3-chloro-phenyl)-pyrazin-2-ylamino]-butan-1-ol;

2-Chloro-6-(5-chloro-2-fluorophenyl)-pyrazine;

{1-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-cyclopentyl}-methanol;

4-[6-((*R*)-1-Hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol;

3-Fluoro-4-[6-(1-hydroxymethyl-propylamino)-pyrazin-2-yl]-phenol;

(1*S*, 2*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol;

(1*R*, 2*S*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol;

(1*R*, 2*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol;

(1*S*, 2*S*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-cyclohexanol;

2-[6-(5-Chloro-thiophen-2-yl)-pyrazin-2-ylamino]-butan-1-ol;

(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(3-fluoro-phenyl)-ethanol;

(*R*)-2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-cyclohexyl-ethanol;

3-Fluoro-4-[6-(1-hydroxymethyl-cyclopentylamino)-pyrazin-2-yl]-phenol;

(*R*)-2-[6-(4-Hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

(*R*)-2-[6-(2-Fluoro-4-hydroxyphenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

3-Fluoro-4-[6-((*R*)-1-hydroxymethyl-2-methyl-propylamino)-pyrazin-2-yl]-phenol;

4-[6-((*R*)-1-Cyclohexyl-2-hydroxy-ethylamino)-pyrazin-2-yl]-3-fluoro-phenol;

2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-(3-bromo-phenyl)-ethanol;

2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-propan-1-ol;

2-Chloro-4-[6-((*R*)-2-hydroxy-1-phenyl-ethylamino)-pyrazin-2-yl]-phenol;

(*R*)-1-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-methyl-1-phenyl-propan-2-ol;

(*R*)-2-[6-(5-Chloro-pyridin-3-yl)-pyrazin-2-ylamino]-2-phenyl-ethanol;

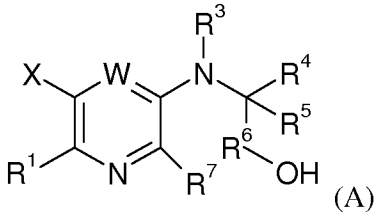
2-[6-(5-Chloro-2-fluoro-phenyl)-pyrazin-2-ylamino]-2-pyridin-3-yl-ethanol;

(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-2-phenyl-ethanol; and

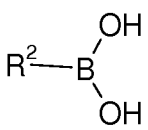
(*R*)-2-[6-(3-Chloro-phenyl)-pyrazin-2-ylamino]-4-methyl-pentan-1-ol.

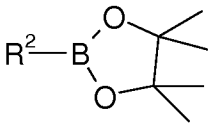
8. A process for the preparation of a compound according to any one of claims 1 to 7 comprising the reaction of

(a) a compound of formula (A)



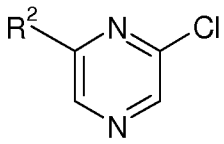
(A)

with 

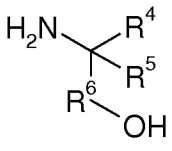
or 

in the presence of a catalyst and a base;

(b) a compound of formula (B)



(B)



with under microwave;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and W are defined above unless otherwise indicated; X is chloro, bromo or iodo.

9. A compound according to any one of claims 1 to 7 for use as therapeutically active substance.

10. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 7 and a therapeutically inert carrier.

11. The use of a compound according to any one of claims 1 to 7 for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers.

12. The use of a compound according to any one of claims 1 to 7 for the treatment of gastric cancer or colorectal cancer.

13. The use of a compound according to any one of claims 1 to 7 for the preparation of a medicament for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers.

14. The use of a compound according to any one of claims 1 to 7 for the preparation of a medicament for the treatment of gastric cancer or colorectal cancer.

15. A compound according to any one of claims 1 to 7 for the treatment of cancer, in particular bladder, head and neck, breast, stomach, ovary, colon, lung, brain, larynx, lymphatic system, liver, skin, hematopoetic system, genitourinary tract, gastrointestinal, ovarian, prostate, gastric, bone, small-cell lung, glioma, colorectal and pancreatic cancers.

16. A compound according to any one of claims 1 to 7 for the treatment of gastric cancer or colorectal cancer.

17. A compound according to any one of claims 1 to 7 as inhibitors of CDK8 or Cyclin C.

18. A compound according to any one of claims 1 to 7, when manufactured according to a process of claim 8.

19. A method for the treatment of cancer, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 7.

20. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/078023

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 C07D401/04 C07D401/12 C07D409/04 C07D241/20
A61K31/4418 A61K31/444 A61K31/4965 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/099796 A1 (CYTOPIA PTY LTD) 4 December 2003 (2003-12-04)	1,2,5,6, 8-16, 18-20
Y	claims; example 18	1-20

X	WO 02/060492 A1 (CYTOPIA PTY LTD) 8 August 2002 (2002-08-08)	1-3,5,6, 9-11,13, 15,18-20
Y	Table 4, compounds 21507, 28608;; claims	1-20

Y	EP 2 138 485 A1 (SANOFI-AVENTIS) 30 December 1999 (1999-12-30) Table 1, compound 2; claims	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2014	11/02/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Helps, Ian

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/078023

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/026904 A1 (NOVARTIS AG) 10 March 2011 (2011-03-10) Reaction schemes 1-12; claims; examples 28, 29	1-3
A	WO 02/096888 A1 (SCHERING) 5 December 2002 (2002-12-05) page 23, line 18 - page 28, line 23; claims; examples	1-20
A	WO 2012/066070 A1 (NOVARTIS AG) 24 May 2012 (2012-05-24) page 1 - page 5; claims; examples	1-20

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