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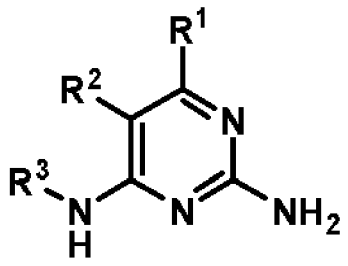

(I)

(57) Abstract: A compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of autoimmune diseases and inflammatory conditions.

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MTH1 INHIBITORS FOR TREATMENT OF INFLAMMATORY AND AUTOIMMUNE CONDITIONS

Field of the Invention

The invention relates to compositions and methods for treatment, prevention and/or prophylaxis of autoimmune diseases and inflammatory (e.g. chronic inflammatory) conditions. In particular, the invention relates to compositions and methods for the treatment and/or prophylaxis of common autoimmune diseases including rheumatoid arthritis, multiple sclerosis and psoriasis through inhibition of MTH1.

Background of the Invention

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

Autoimmune and inflammatory disorders

Autoimmune diseases and hyperinflammatory disorders are conditions where a mammal's immune system starts reacting against its own tissues. Such conditions include, without limitation, arthritis, e.g. rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

Shortcomings and complications with current treatment

Today's treatment of inflammatory and autoimmune diseases and disorders is not effective for all patients with diagnosed disease also including a large proportion of patients that experience adverse effects from treatments with existing therapies.

Today's treatment of autoimmune conditions like RA is not effective for all patients with diagnosed disease also including a large proportion of patients that experience adverse effects from treatments with biological agents, as represented by the therapy with TNF-α inhibitors, or from treatment with Methotrexate and COX-2 inhibitors. In similarity to RA, the cause and pathology of autoimmune and (hyper) inflammatory conditions including MS, IBD and the majority of less prevalent autoimmune conditions, is far from understood and many patients suffer from a disease that current treatments do not have the capacity to treat or ameliorate, hence there is a great need to understand the mechanisms driving these diseases which will enable novel ways for treatments.

The present invention aims at providing new treatments for inflammatory and autoimmune diseases based on immunomodulatory effects that can be achieved by inhibition of the MTH1 enzyme.

Prior art

Engelhardt, H. *et al. Journal of Medicinal Chemistry* (2013), 56(11), 4264-4276 discloses certain 6-aryl-2,4-diaminopyrimidines having an additional pyrimidine appendage as histamine H4 receptor modulators. The paper suggests that the compounds are useful for the treatment of e.g. immune and inflammatory conditions, but there are no data that supports such statements. The only 6-aryl compounds that are exemplified or mentioned are phenyl or 3-chlorophenyl and there is nothing that suggests that any particular substitution pattern, e.g. 2,3-disubstituted phenyls, or heteroaryls, would be particularly advantageous.

US patent application US 2010/0016344 disclose certain 6-aryl-2,4-diamino-pyrimidines having an additional pyrimidine appendage as histamine H4 receptor modulators. The compounds are claimed to be useful for the treatment of e.g. autoimmune and inflammatory disorders. Data supporting the usefullness in the

treatment of inflammatory pain is presented. There is no support that the compounds would be effective in the treatment of autoimmune diseases in general. The preferred 6-aryl is stated to be phenyl or 3-chlorophenyl although also 3,5-dichlorophenyl and 5-chloro-5-methoxyphenyl are exemplified. However, there is nothing that suggests that 2,3-disubstituted phenyls would be particularly advantageous.

International patent application WO 2013/066839 discloses three 6-(3-pyridyl)-(2,4-diaminopyrimidines as HDAC inhibitors. However, the 3-pyridyl is unsubstituted and there is nothing that suggests that replacing them with other heteroaryls or substituted phenyls would be advantageous. Moreover, the substituent on the 4-amino group contains an essential 5-trifluoromethyl-1,2,4-oxadiazol-3-yl group.

International patent application WO 2005/066839 discloses benzamides which are necessarily substituted in the 2-position by hydroxy or amino. In one case this moiety is linked to the 4-amino group of a 2,4-diamino-6-(3-pyridyl)pyrimidine. The compounds are stated to be useful in the treatment of cell prolifeartive diseases and conditions. Autoimmune or inflammatory disorders are not mentioned or suggested.

International patent application WO 2010/059658 describes 2,4-diamino-pyrimidines substituted in the 6-position with 6-indazolyl or 3-cyano-2-fluorophenyl, where the latter is just a synthetic precursor to the former. In addition, the relevant indazoles all carry a 3-amino substituent. Although immune diseases are mentioned in the text, there are no data to support the usefulness of the compounds for such diseases; the only claimed use is for cancer. The same compounds are also discussed in and J.R. Medina *Journal of Medicinal Chemistry* (2011), 54, 1871-1895, where it is stated that the compounds only modestly inhibits tumor growth *in vivo*.

International patent application WO 2006/078886 describes 2,4-diamino-pyrimidines substituted in the 6-position by phenyl and where the 4-amine is substituted by an arylalkyl or heteroarylalkyl group. The phenyl must be unsubstituted or have one or more alkoxy substituents. The arylalkyl and

heteroarylalkyl must be unsubstituted or have one or more halogens, cyano and/or hydroxy. The compounds are claimed to be useful to treat disorders where wnt-signalling is involved, but inflammatory or auto-immune disorders are not mentioned.

International patent application WO 2005/026129 discloses 4,6-disubstituted aminopyrimidines as protein kinase modulators useful in the treatment of e.g. inflammation an autoimmune diseases. Of the 385 examples only two are 2,4-diaminopyrimidines and both these have a phenyl attached directly to the 4-amino group of the pyrimidine. These phenyls also carry an additional 4-aminosubstituent.

Two publications from the group of H. Junjappa (*Indian Journal Chemistry* (1985), 24B 466; *Synthesis* (1980), 748) describes the synthesis of certain 2-amino-4-(*N*-alkylamino)-6-arylpyrimidines. The publications do not mention or suggest the use of the synthesized compounds in the treatment of autoimmune and inflammatory disorders.

Japanese patents JP49021147 and JP49021148 disclose certain 2-amino-4-(*N*-alkylamino)-6-(pyridyl)pyrimidines claimed to be anti-inflammatory. There is however no data to support this claim. Also, all pyridines are unsubstituted and there is nothing that indicates that substituents on the pyridines would be beneficial.

There are numerous 2-amino-4-(*N*-alkylamino)-6-arylpyrimidines that are, or that at some point have been stated to be, commercially available but that do not have any ascribed pharmaceutical use ascribed to them.

MTH1 inhibitors have been described in Streib, M. *et al. Angewandte Chemie, Int,. Ed.* (2014), 52, 305-309. The compounds are organometallic and are not substituted 2,4-diaminopyrimidines.

Huber, K.V.M. *et al. Nature* (2014), 508, 222-227 describe certain compounds, i.e. (S)-crizotinib, as MTH1 inhibitors. However, the compounds are not substituted 2,4-diaminopyrimidines.

Gad, H. *et al. Nature* (2014), 508, 215-221 and Saleh, A. *et al. Journal of Pharmaceutical and Biomedical Analysis* (2015), 104, 1, describe certain 2,4-diaminopyrimidines as MTH1 inhibitors. However, there is nothing that suggests that the compounds are useful for treatment of inflammatory or auto-immune diseases.

International patent application WO 2013/066839 discloses certain 6-aryl-2,4-diaminopyrimidines, which may be useful in the treatment of cancer.

Chinese patent application CN104288170 describes the natural product echinacoside as an inhibitor of MTH1. However this compound is a sugar derivative and not a pyrimidine

Kambe, T. *et al. Journal of the American Chemical Society* (2014), 136, 10777 demonstrate a tetrazole-based MTH1 ligand.

Summary of the invention

In autoimmune conditions and after organ transplantation, it is vital to eliminate the activated auto-reactive lymphocytes while preferably preserving their normal counterparts. Inhibiting MTH1 activity will kill the activated lymphocytes and thus reduce destructive inflammation. It should therefore be a promising novel therapy for autoimmunity and organ rejection, either as monotherapy or in combination with other drugs (e.g. cortisone) that are currently on the market.

We have observed that silencing the enzymatic activity of MTH1 in human lymphocytes results in selective killing of activated lymphocytes. Resting lymphocytes are not affected by the treatment. The present invention aims at providing a new treatment option for autoimmune conditions and transplantation patients through pharmacologic inhibition of MTH1. Diseases which may benefit from this treatment include rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune

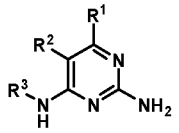
uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

Brief description of the drawings

Figure 1. An MTH1 inhibitor (example 297) selectively kills activated T-lymphocytes while unactivated T-lymphocytes are unaffected.

Detailed description of the Invention

There is provided a compound of formula I,

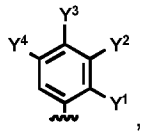


(I)

or a pharmaceutically acceptable salt thereof,

for use in the treatment of autoimmune diseases and inflammatory conditions, wherein:

R^1 represents

(i)  , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, or

(iv) -ethynyl-Y^6;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2; or

R^1 represents

(v) a 3- to 8-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J; or

R^1 is as defined herein above; and

R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more groups selected from Z^3 and optionally substituted by -X-L-J;

X represents -C_{1-6}alkylene-, optionally substituted by one or more T^1, or -$(C(R^A)_2)_p$-C_{2-5}heterocycloalkylene-$(C(R^A)_2)_q$-, where the heterocycloalkylene is optionally substituted by one or more T^2;

L represents a single bond or -L^1-L^2-;

L^1 represents -$N(R^B)$-, -O-, -$S(O)_m$-, -$C(O)N(R^C)$-, -$N(R^D)C(O)$-, -$S(O)_nN(R^E)$-, -$N(R^F)S(O)_n$- or -$N(R^G)C(O)N(R^H)$-;

L^2 represents a single bond or -C_{1-6}alkylene-;

J represents

(i) a 6- to 10-membered aryl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or

(ii) a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which heteroaryl is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

Y^1 represents hydrogen, halogen, -CN, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S($NR^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -O$R^m$ -SR^n;

Y^2, Y^3 and Y^4 each independently represents hydrogen, halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S($NR^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -OH, -O$R^m$ or -SR^n;

Y^5 represents halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S($NR^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -OH, -O$R^m$ or -SR^n;

Y^6 represents aryl or heteroaryl, both optionally substituted by one or more groups selected from halogen, -CN, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S($NR^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -OH, -O$R^m$ and -SR^n;

Y^7 represents halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -OH, -O$R^m$, or Q;

Q represents =O, =S, =NR^o, =NN(R^p)R^q, =N(OR^r), =NS(O)$_2$N(R^s)R^t or =C(H)NO_2;

A represents a single bond, -N(R^l)-, -C(Q)N(R^J)- or -O-;

each R^a, R^f, R^h and R^m independently represents C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3;

each R^b, R^c, R^d, R^e, R^g, R^i, R^j, R^k, R^l, R^o, R^p, R^q, R^r, R^s and R^t independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3; or

any two R^c and R^d, R^i and R^j, R^p and R^q and/or R^s and R^t are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more groups selected from W^2, C_{1-3}alkyl optionally substituted by one or more groups selected from W^1, and =O; or

two R^l are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

W^1 represents halogen, -CN, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$,$-OR^{j1}$ or =O;

W^2 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$, $-OR^{j1}$ or =O;

W^3 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-OR^{j1}$, $-A^1-S(NR^{k1})(O)R^{l1}$, $-A^1-S(O)_nN(R^{m1})R^{n1}$, $-N_3$, $-NO_2$, $-SR^{o1}$ or =O;

A^1 represents a single bond, $-N(R^K)-$ or -O-;

each R^{a1}, R^{f1} and R^{l1} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1} and R^{o1} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro; or

any two R^{c1} and R^{d1}, R^{h1} and R^{i1} and/or R^{m1} and R^{n1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is

substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

Z^1 represents halogen, -CN, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$, $-SR^{o2}$ or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

Z^2 represents halogen, -CN, R^{a2}, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or $=Q^1$;

Z^3 represents R^{a2} or $=Q^1$;

Q^1 represents =O, =S, $=NR^{p2}$, $=NN(R^{q2})R^{r2}$, $=N(OR^{s2})$, $=NS(O)_2N(R^{t2})R^{u2}$ or $=C(H)NO_2$;

A^2 represents a single bond, $-N(R^L)-$, $-C(Q^1)N(R^M)-$ or -O-;

each R^{a2}, R^{f2}, R^{i2}, R^{n2} and R^{o2} independently represents C_{1-6}alkyl optionally substituted by one or more groups selected from W^4 or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

R^{m2} represents C_{2-6}alkyl optionally substituted by one or more groups selected from W^4;

each R^{b2}, R^{c2}, R^{d2}, R^{e2}, R^{g2}, R^{h2}, R^{j2}, R^{k2}, R^{l2}, R^{p2}, R^{q2}, R^{r2}, R^{s2}, R^{t2} and R^{u2} independently represents hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from W^4, heterocycloalkyl optionally substituted by one or more groups selected from W^5; or

any two R^{c2} and R^{d2}, R^{j2} and R^{k2}, R^{l2} and R^{m2}, R^{q2} and R^{r2} and/or R^{t2} and R^{u2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more

groups selected from W^5, C_{1-3}alkyl optionally substituted by one or more groups selected from W^4, and =O;

W^4 represents halogen, -CN, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^5 represents halogen, -CN, R^{a3}, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^6 represents phenyl or heteroaryl, both optionally substituted by one or more groups selected from halogen and R^{a3};

A^3 represents a single bond, $-N(R^L)-$ or -O-;

each R^{a3} and R^{f3} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{g3} and R^{h3} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

R^{c3} and R^{d3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatoms and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

D^1 and D^2 represent R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nC(O)R^{g4}$, $-A^4-S(NR^{h4})(O)R^{i4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-A^4-S(O)_nOR^{l4}$, $-B(OR^{m4})_2$, $-N_3$, $-N(R^{n4})R^{o4}$, -N(H)CN, $-NO_2$, $-ONO_2$, $-OR^{p4}$, $-SR^{q4}$ or, when J is partly aromatic, $=Q^2$;

Q^2 represents =O, =S, $=NR^{r4}$, $=NN(R^{s4})R^{t4}$, $=N(OR^{u4})$, $=NS(O)_2N(R^{v4})R^{w4}$ or $=C(H)NO_2$;

A^4 represents a single bond, $-N(R^M)-$, $-C(Q)N(R^N)-$ or -O-;

each R^X and R^Y independently represent halogen, -CN, R^{a4}, $-N(R^{n4})R^{o4}$, $-NO_2$, $-OR^{p4}$ or =O;

R^{c4} represents hydrogen, R^{a4}, $-C(O)OR^{e4}$, $-S(O)_nR^{f4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$ or $-OR^{p4}$;

each R^{a4}, R^{f4} and R^{i4} independently represent C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

each R^{b4}, R^{d4}, R^{e4}, R^{g4}, R^{h4}, R^{j4}, R^{k4}, R^{l4}, R^{m4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4}, R^{s4}, R^{t4}, R^{u4}, R^{v4} and R^{w4} independently represent hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, R^{n4} and R^{o4}, R^{s4} and R^{t4} and/or R^{v4} and R^{w4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one heteroatom and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O; or

two R^{m4} are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each G^1 is independently selected from halogen, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^2 is independently selected from halogen, R^{a5}, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^3 and G^4 are independently selected from halogen, -CN, R^{a5}, $-N(R^{b5})R^{c5}$, $-A^5-C(O)R^{d5}$, $-A^5-C(O)N(R^{e5})R^{f5}$, $-A^5-C(O)OR^{g5}$, $-A^5-S(O)_nR^{h5}$, $-A^5-S(O)_nN(R^{i5})R^{j5}$, $-OR^{k5}$ or =O;

A^5 represents a single bond or -N(H)-;

R^{a5} represents C_{1-6} alkyl optionally substituted by one or more halogens;

each R^{b5}, R^{c5}, R^{d5}, R^{e5}, R^{f5}, R^{g5}, R^{h5}, R^{i5}, R^{j5}, R^{k5} and R^{l5} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more halogens; or

any two R^{b5} and R^{c5}, R^{e5} and R^{f5} and/or R^{i5} and R^{j5} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each R^A, R^B, R^C, R^D, R^E, R^F, R^G, R^H, R^I, R^J, R^K, R^L, R^M and R^N independently represents hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro;

T^1 represents halogen, -CN, $-N(R^{b6})R^{c6}$ or $-OR^{d6}$;

T^2 represents halogen, -CN, R^{a6}, $-OR^{d6}$ or =O;

each R^{a6} independently represents C_{1-6}alkyl optionally substituted by one or more halogens;

each R^{b6}, R^{c6} and R^{d6} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more halogens; or

R^{b6} and R^{c6} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring;

each p and q independently represents 0, 1 or 2, provided that the sum of p and q is 0, 1 or 2;

each m independently represents 0, 1 or 2;

each n independently represents 1 or 2;

provided that when X represents $-CH_2CH_2-$, L represents $-L^1-L^2-$, L^1 represents -N(H)- or -N(Me)-, L^2 represents a single bond and J represents 4-pyrimidinyl, and said 4-pyrimidinyl is unsubstituted or substituted with $-CH_3$, $-NH_2$ or $-N(H)CH_2CH(CH_3)_2$, then R^1 does not represent phenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 5-chloro-2-methoxyphenyl, and

provided that formula I does not represent (*S*)-*N*^{4}-(1-(2,4-difluorophenyl)ethyl)-6-(pyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidine-2,4-diamine.

The compounds of formula (I) as defined herein above may be referred to herein as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin. For the avoidance of doubt, solvates are also included within the scope of the invention.

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double

bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

The terms "halo" or "halogen", when used herein, includes fluoro, chloro, bromo and iodo (for example, fluoro and chloro).

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Part cyclic alkyl groups that may be mentioned include cyclopropylmethyl and cyclohexylethyl. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

Unless otherwise specified, C_{1-q} alkylene groups (where q is the upper limit of the range) defined herein may (in a similar manner to the definition of C_{1-q} alkyl) be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkylene group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkylene groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q}alkenylene or a C_{2-q}alkynylene group). Particular alkylene groups that may be mentioned include those that are straight-chained or cyclic and saturated.

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten and, most preferably, between three and eight, e.g. a 5- or 6-membered heterocycloalkyl group). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} (e.g. C_{4-q}) heterocycloalkenyl (where q is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo-[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidinyl, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), 1,3,2-dioxaborinane, 1,3,6,2-dioxazaborocane, 1,3,2□dioxaborolane, dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, tetrahydrothiopyranyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where

appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. At each occurrence when mentioned herein, a heterocycloalkyl group is preferably a 3- to 8-membered heterocycloalkyl group (e.g. a 5- or 6-membered heterocycloalkyl group).

The term "aryl", when used herein, includes C_{6-10} aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C_{6-10} aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (e.g. phenyl, naphthyl and the like). For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

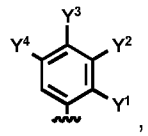
The term "heteroaryl" (or heteroaromatic), when used herein, includes 5- to 11-membered heteroaromatic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur. Such heteroaryl group may comprise one, or two rings, of which at least one is aromatic. Substituents on heteroaryl/hetero-aromatic groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl/hetero-aromatic groups may be *via* any atom in the ring system including (where appropriate) a heteroatom. Bicyclic heteroaryl/heteroaromatic groups may comprise a benzene ring fused to one or more further aromatic or non-aromatic heterocyclic rings, in which instances, the point of attachment of the polycyclic heteroaryl/heteroaromatic group may be *via* any ring including the benzene ring or the heteroaryl/heteroaromatic or heterocycloalkyl ring. Examples of heteroaryl/heteroaromatic groups that may be mentioned include pyridinyl, pyrrolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, imidazothiazolyl, thienothiophenyl, pyrimidinyl, furopyridinyl, indolyl, azaindolyl, pyrazinyl, indazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl,

benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl and purinyl. The oxides of heteroaryl/ heteroaromatic groups are also embraced within the scope of the invention (e.g. the *N*-oxide). As stated above, heteroaryl includes polycyclic (e.g. bicyclic) groups where all rings are aromatic, and partly aromatic groups where at least one ring is aromatic and at least one other ring is not aromatic. Hence, other heteroaryl groups that may be mentioned include e.g. benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, dihydrobenzo[*d*]isothiazolyl, 1,2-dihydrobenzo[*d*][1,2,3]diazaborininyl, 3,4-dihydro-1*H*-benzo[*c*][1,2]oxaborininyl, 1,3-dihydrobenzo[*c*][1,2]oxaborolyl, 3,4-dihydrobenz[1,4]oxazinyl, dihydrobenzothiophene, indolinyl, *5H,6H,7H*-pyrrolo[1,2-*b*]pyrimidinyl, 1,2,3,4-tetrahydroquinolinyl, thiochromane and the like.

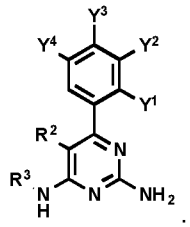
Heteroatoms that may be mentioned include phosphorus, silicon, preferably boron and, more preferably, oxygen, nitrogen and sulfur.

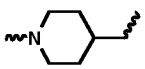
For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent.

For the avoidance of doubt, when R^1 is defined as

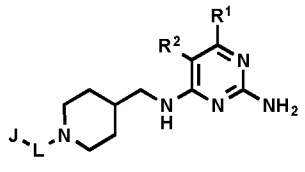


it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by

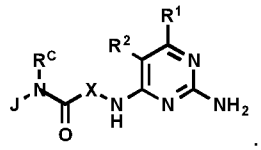


For the avoidance of doubt, when R^3 represents -X-L-J, X represents $-(C(R^A)_2)_p-C_{2-5}$heterocycloalkylene$-(C(R^A)_2)_q-$, R^A represents hydrogen, p represents 1 and q represents 0, then $-(C(R^A)_2)_p-C_{2-5}$heterocycloalkylene$-(C(R^A)_2)_q-$ may represent e.g. 

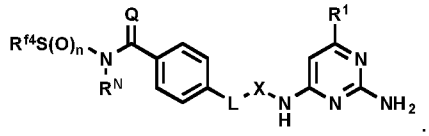
, and formula I can then be represented by



Likewise, when R^3 represents -X-L-J, L represents $-L^1-L^2-$, L^1 represents $-C(O)N(R^C)-$ and L^2 represents a single bond, then formula I can be represented by



Likewise, when J is phenyl substituted in the 4-position by D^1, D^1 is $-A^4-S(O)_nR^{f4}$ and A^4 represents $-C(Q)N(R^N)-$, then formula I can be represented by

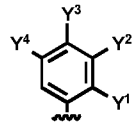


The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Hence, the compounds of the invention also include deuterated compounds, i.e. in which one or more hydrogen atoms are replaced by the hydrogen isotope deuterium.

All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred features) mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

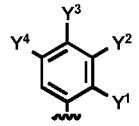
The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

In some embodiments of the invention, R^1 represents (i)



wherein Y^1, Y^2, Y^3 and Y^4 are as defined herein above.

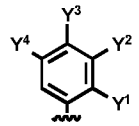
Particular compounds of formula I that may be mentioned include those in which R^1 represents


;

Y^1 in particular may represent hydrogen, halogen, -CN, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(N$R^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -O$R^m$, -S$R^n$; and

Y^2, Y^3 and Y^4 in particular may each independently represent hydrogen, halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(N$R^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -OH, -O$R^m$ or -SR^n.

When R^1 represents


,

one of Y^1, Y^2, Y^3 and Y^4 is preferably other than hydrogen, or more preferably, two or three of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

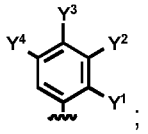
R^2 represents methyl, or preferably, hydrogen;

R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2;

Y^1 represents halogen, -CN, R^a or -OR^m; and

Y^2, Y^3 and Y^4 each independently represent hydrogen, halogen, R^a, -A-C(Q)R^b, -C(Q)N(R^c)R^d, -C(Q)OR^e, -A-S(O)$_n$$R^f$, -S(O)$_n$N($R^i$)$R^j$, -OH or -O$R^m$.

Preferred compounds of formula I that may be mentioned include those in which R^1 represents



;

Y^2, Y^3 and Y^4 represent hydrogen; and

Y^1 represents fluoro, chloro, $-CH_3$, $-CF_3$, -CN, CH_2OH or $-OCH_3$; or

Y^1, Y^3 and Y^4 represent hydrogen; and

Y^2 represents fluoro, chloro, $-CH_3$, $-CF_3$, $-CH=CHC(O)OCH_3$, $-CH_2NH_2$, -CN, $-CH_2N(H)C(O)CH=CH_2$, $-CH_2OH$, $-C(O)N(H)$(4-methylphenyl), $-N(H)C(O)CH_3$, $-N(H)C(O)CH=CH_2$, $-N(H)C(O)CH=CHCH_2NMe_2$, $-N(H)C(O)CH=CHPh$, $-N(H)C(O)C\equiv CH$, $-N(H)C(O)$(2-hydroxyphenyl), $-N(H)C(O)$(6-hydroxypyrid-2-yl), $-N(H)C(O)$(5-chloro-2-hydroxyphenyl), $-N(H)C(O)CH_2CH_2C(O)$(1-pyrrolidinyl), $-N(H)C(O)CH_2(OH)$, $-N(H)C(O)CH(OH)Ph$, $-N(H)C(O)C(O)CH_3$, $-N(H)C(O)C(O)Ph$, $-N(H)S(O)_2CH=CH_2$, -OH, $-OCH_3$, $-OCH_2C(O)NH_2$ or $-OSO_2CF_3$; or

Y^1, Y^2 and Y^4 represent hydrogen; and

Y^3 represent fluoro, chloro, $-CH_3$, $-CF_3$, $-C(CH_3)_3$, $-CH=CH_2$, $-CH=CHC(O)OH$, $-CH=CHC(O)OCH_3$, $-CH_2NH_2$, -CN, $-CH_2N(H)C(O)CH=CH_2$, $-CH_2OH$, $-C(O)H$, $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)N(H)CH_3$, $-C(O)N(H)CH_2$(2-furanyl), $-C(O)$(4-morpholinyl), $-C(O)OH$, $-C(O)OCH_3$, $-N(H)C(O)CH_3$, $-N(H)C(O)CH=CH_2$, $-N(H)S(O)_2CH_3$, $-OCH(CH_3)_2$, $-OCH_3$, $-OCF_3$, $-S(O)_2CH_3$, or $-S(O)_2$(4-morpholinyl); and

R^2 represents methyl, or preferably, hydrogen;

R^3 represents -X-L-J or $-C_{1-6}$alkyl optionally substituted by one or more, preferably one to three, groups selected from Z^1, or heterocycloalkyl optionally substituted by one or more, preferably one to three, groups selected from Z^2;

X represents $-C_{1-6}$alkylene- optionally substituted by T^1, or $-(C(R^A)_2)_p-C_{2-5}$heterocycloalkylene-$(C(R^A)_2)_q-$;

L represents a single bond or $-L^1-L^2-$;

L^1 represents -N(H)-, -O-, $-SO_2-$, -C(O)N(H)-, $-S(O)_nN(H)-$ or -N(H)C(O)N(H)-;

L^2 represents a single bond or $-C_{1-6}$alkylene-;

J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or a 5- to 10-membered monocyclic or bicyclic heteroaryl containing 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one sulfur atom and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

Z^1 represents halogen, -CN, $-A^2-C(O)R^{b2}$, $-A^2-C(O)N(R^{c2})R^{d2}$, $-A^2-C(O)OR^{e2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or heterocycloalkyl optionally substituted by =O;

Z^2 represents R^{a2}, $-C(O)OR^{e2}$ or =O;

T^1 represents $-N(R^{l2})R^m$;

A^2 represents a single bond or -N(H)-;

D^1 represents R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-SO_2N(R^{j4})R^{k4}$, $-SO_2OR^{l4}$, $-N(R^{n4})R^{o4}$, -N(H)CN, $-NO_2$, $-OR^{p4}$ or $-SR^{q4}$;

D^2 represents R^{a4}, $-A^4-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$, $-NO_2$, or $-OR^{p4}$;

Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$;

A^4 represents a single bond or -N(H)-;

each R^X and R^Y independently represent halogen, -CN, R^{a4} or $-OR^{p4}$;

R^{a4} represents C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, phenyl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

R^{c4} represents hydrogen, R^{a4} or $-C(O)OR^{e4}$;

R^{b4} and R^{f4} represent C_{1-6}alkyl optionally substituted by one or more fluoro;

each, R^{d4}, R^{e4}, R^{j4}, R^{k4}, R^{l4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4} and R^{u4} independently represent hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, and/or R^{n4} and R^{o4} are linked together to form, along with the nitrogen atom to which they are attached, a 4- to 6-membered ring;

each G^1 independently represent one or more halogens;

each G^3 and G^4 independently represent one or more more groups selected from halogen, R^{a5} or $-OR^{k5}$;

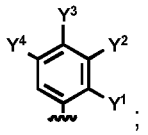
R^{a5} represents C_{1-6} alkyl optionally substituted by one or more fluoro;

R^{k5} represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro;

each p and q independently represents 0 or 1, provided that the sum of p and q is 0 or 1; and

each n independently represents 1 or 2.

Other preferred compounds of formula I that may be mentioned include those in which R^1 represents



;

Y^3 and Y^4 represent hydrogen; and

Y^1 represents fluoro and Y^2 represent fluoro, chloro, $-CH_3$ or $-CF_3$; or

Y^1 represents chloro and Y^2 represents fluoro, chloro, $-CH_3$ or $-CF_3$; or

Y^1 represents $-CH_3$ and Y^2 represents fluoro, chloro, $-CH_3$, $-CF_3$, -CN

-N(H)C(O)CH=CH_2 or -N(H)C(O)(4-chloro-2-hydroxyphenyl); or

Y^2 and Y^4 represent hydrogen; and

Y^1 represents fluoro and Y^3 represents fluoro or phenyl; or

Y^1 represents chloro and Y^3 represents fluoro, chloro; or

Y^1 represents $-CH_3$ and Y^3 represents chloro or $-OCH_2$phenyl; or

Y^1 represents $-OCH_3$ and Y^3 represents fluoro; or

Y^2 and Y^3 represent hydrogen; and

Y^1 represents fluoro and Y^4 represents chloro, $-CH_3$ or -CN; or

Y^1 represents chloro and Y^4 represent fluoro, chloro, $-CH_3$, $-CF_3$ or $-OCH_3$; or

Y^1 represents $-CH_3$ and Y^4 represent fluoro, chloro, $-CH_3$, $-CF_3$, -CN,

-N(H)C(O)CH=CH_2 or -$S(O)_2$(4-morpholinyl); or

Y^1 represents $-CF_3$ and Y^4 represents fluoro or $-CF_3$; or

Y^1 represents -CN and Y^4 represents chloro; or

Y^1 represents $-OCH_3$ and Y^4 represents fluoro, chloro, bromo, $-CH_3$, $-CH(CH_3)_2$,

$-C(CH_3)_3$, -CN or $-OCH_3$; or

Y^1 and Y^4 represent hydrogen; and

Y^2 represents fluoro and Y^3 represents fluoro, chloro, -OH or $-OCH_3$; or

Y^2 represents chloro and Y^3 represents fluoro or -C(O)(4-morpholinyl); or

Y^2 represents $-CH_3$ and Y^3 represents fluoro or $-OCH_3$; or

Y^1 represents $-OCH_3$ and Y^3 represents -OH; or

Y^1 represents-CH_2OCH_3 and Y^3 represents (piperidin-4-yl)methoxy or

((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or

Y^1 and Y^3 represent hydrogen; and

Y^2 and Y^4 represent fluoro; or

Y^2 and Y^4 represent $-CF_3$; or

Y^4 represents hydrogen; and

Y^1, Y^2 and Y^3 represent fluoro or chloro; or
Y^1 and Y^2 represent chloro and Y^3 represents chloro, -OH or $-OCH_3$; or
Y^1 and Y^2 represent $-CH_3$ and Y^3 represents fluoro or $-OCH_3$; or
Y^1 and Y^3 represent chloro and Y^2 represents $-OCH_3$; or
Y^2 and Y^3 represent chloro and Y^1 represents $-CH_3$; or

Y^2 represents hydrogen; and
Y^1, Y^3 and Y^4 represent fluoro; or
Y^3 and Y^4 represent chloro and Y^1 represents $-CH_3$; or
Y^1 and Y^4 represent chloro and Y^1 represents $-OCH_3$; or
Y^1 and Y^4 represent $-CH_3$ and Y^3 represents fluoro, $-CH_3$ or $-OCH_3$; or
Y^1 represents fluoro, Y^3 represents $-CH_3$ and Y^4 represents chloro; or
Y^1 represents chloro, Y^3 represents fluoro and Y^4 represents $-CH_3$; or
Y^1 represents chloro, Y^3 represents $-CH_3$ and Y^4 represents fluoro; or
Y^1 and Y^4 represent $-CH_3$ and Y^3 represents fluoro; or
Y^1 represents $-CH_3$, Y^4 represents chloro and Y^3 represents $-CF_3$ or $-OCH_3$; or

Y^1 represents hydrogen; and
Y^2 and Y^4 represent $-CH_3$ and Y^3 represents -OH; or

Y^3 represents hydrogen; and
Y^1 and E^2 represent chloro and Y^4 represents $-CH_3$;

R^2 represents methyl, or preferably, hydrogen;
R^3 represents -X-L-J or C_{1-6}alkyl optionally substituted by one or more, preferably one to three groups selected from Z^1, or heterocycloalkyl optionally substituted by one or more, preferably one to three, groups selected from Z^2;
X represents C_{1-6}alkylene- optionally substituted by T^1, or
$-(C(R^A)_2)_p-C_{2-5}$heterocycloalkylene-$(C(R^A)_2)_q-$;
L represents $-L^1-L^2-$;
L^1 represents -N(H)-, -O-, $-SO_2-$, -C(O)N(H)-, $-S(O)_nN(H)-$ or -N(H)C(O)N(H)-;
L^2 represents a single bond or $-C_{1-6}$alkylene-;
J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or a 5- to 10-membered monocyclic or bicyclic heteroaryl having 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one

sulfur atom and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

Z^1 represents halogen, -CN, $-A^2-C(O)R^{b2}$, $-A^2-C(O)N(R^{c2})R^{d2}$, $-A^2-C(O)OR^{e2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or heterocycloalkyl optionally substituted by =O;

A^2 represents a single bond or -N(H)-;

Z^2 represents R^{a2}, $-C(Q^1)OR^{e2}$ or =O;

D^1 represents R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-SO_2N(R^{j4})R^{k4}$, $-SO_2OR^{l4}$, $-N(R^{n4})R^{o4}$, -N(H)CN, $-NO_2$, $-OR^{p4}$ or $-SR^{q4}$;

D^2 represents R^{a4}, $-A^4-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$, $-NO_2$, or $-OR^{p4}$;

Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$;

A^4 represents a single bond or -N(H)-;

each R^X and R^Y independently represent halogen, -CN, R^{a4} or $-OR^{p4}$;

R^{a4} represents C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, phenyl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

R^{c4} represents hydrogen, R^{a4} or $-C(O)OR^{e4}$;

R^{b4} and R^{f4} represent C_{1-6}alkyl optionally substituted by one or more fluoro;

each R^{d4}, R^{e4}, R^{j4}, R^{k4}, R^{l4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4} and R^{u4} independently represent hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, and/or R^{n4} and R^{o4} are linked together to form, along with the nitrogen atom to which they are attached, a 4- to 6-membered ring;

each G^1 independently represent one or more halogens;

each G^3 and G^4 independently represent one or more more groups selected from halogen, R^{a5} or $-OR^{k5}$;

R^{a5} represents C_{1-6} alkyl optionally substituted by one or more fluoro;

R^{k5} represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro;

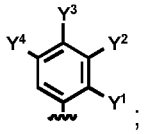
T^1 represents $-N(R^{b6})R^{c6}$ or $-OR^{d6}$;

each R^{b6}, R^{c6} and R^{d6} independently represents hydrogen or $-C_{1-6}$alkyl;

each p and q independently represents 0 or 1, provided that the sum of p and q is 0 or 1; and

each n independently represents 1 or 2.

Particularly preferred compounds of formula I that may be mentioned include those in which R^1 represents



;

Y^1, Y^3 and Y^4 represent hydrogen; and

Y^2 represents -CH=CHC(O)OCH_3, -CH_2NH_2, -CH_2N(H)C(O)CH=CH_2, -CH_2OH, -N(H)C(O)CH=CH_2, -N(H)C(O)CH=CHCH_2NMe_2, -N(H)C(O)CH=CHPh, -N(H)C(O)C≡CH, -N(H)C(O)CH_2(OH), -N(H)C(O)CH(OH)Ph, -N(H)C(O)C(O)CH_3, -N(H)C(O)C(O)Ph or -N(H)$S(O)_2CH=CH_2$; or

Y^1, Y^2 and Y^4 represent hydrogen and

Y^3 represents -CH=CH_2, -CH=CHC(O)OH, -CH=CHC(O)OCH_3, -CH_2NH_2, -CH_2N(H)C(O)CH=CH_2, -CH_2OH, -C(O)H, -C(O)CH_3, -C(O)CF_3, -N(H)C(O)CH=CH_2; or

Y^3 and Y^4 represent hydrogen; and

Y^1 represents fluoro and Y^2 represents fluoro, chloro, or -CF_3; or

Y^1 represents -Cl and Y^2 represents v, -CH_3 or -CF_3; or

Y^1 represents -CH_3 and Y^2 represents chloro, -CH_3, -CF_3, -CN or -N(H)C(O)CH=CH_2; or

Y^2 and Y^4 represent hydrogen; and

Y^1 and Y^3 represent fluoro; or

Y^1 represents chloro and Y^3 represents fluoro or chloro; or

Y^1 represents -CH_3 and Y^3 represents chloro; or

Y^2 and Y^3 represent hydrogen; and

Y^1 represents fluoro and Y^4 represents chloro, -CH_3 or -CN; or

Y^1 represents chloro and Y^4 represents fluoro, chloro, -CH_3 or -CF_3; or

Y^1 represents -CH_3 and Y^4 represent, chloro, -CH_3, -CF_3, -CN or -N(H)C(O)CH=CH; or

Y^1 represents -CF_3 and Y^4 represents fluoro or -CF_3; or

Y^1 represents -CN and Y^4 represents chloro; or

Y^4 represents hydrogen; and

Y^1, Y^2 and Y^3 represent fluoro; or

Y^1 and Y^2 represent -CH_3 and Y^3 represents fluoro; or

Y^2 and Y^3 represent chloro and Y^1 represents $-CH_3$; or

Y^2 represents hydrogen; and
Y^1, Y^3 and Y^4 represent fluoro; or
Y^3 and Y^4 represent chloro and Y^1 represents $-CH_3$; or
Y^1 and Y^4 represent $-CH_3$ and Y^3 represents fluoro or $-CH_3$; or
Y^1 represents fluoro, Y^3 represents $-CH_3$ and Y^4 represents chloro; or
Y^1 represents chloro, Y^3 represents -F and Y^4 represents $-CH_3$; or
Y^1 represents chloro, Y^3 represents $-CH_3$ and Y^4 represents fluoro; or
Y^1 and Y^4 represent $-CH_3$ and Y^3 represents fluoro; or
Y^1 represents $-CH_3$, Y^3 represents $-CF_3$ and Y^4 represents chloro; or

Y^1 represents hydrogen; and
Y^2 and Y^4 represent $-CH_3$ and Y^3 represents -OH; or

Y^3 represents hydrogen; and
Y^1, Y^2 and Y^4 represent chloro; or
Y^1 and Y^2 represent chloro and Y^4 represents $-CH_3$;

In some embodiments of the invention R^2 represents methyl, or preferably, hydrogen;
R^3 represents -X-L-J or $-C_{1-6}$alkyl optionally substituted by one to three groups selected from Z^1, or heterocycloalkyl optionally substituted by Z^2;
X represents $-C_{1-6}$alkylene-;
L represents $-L^1-L^2-$;
L^1 represents -N(H)-, -O-, -C(O)N(H)-, $-S(O)_nN(H)-$ or -N(H)C(O)N(H)-;
L^2 represents a single bond;
J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or a 5- to 10-membered monocyclic or bicyclic heteroaryl having 1 to 3 nitrogen atoms and/or one oxygen atom and/or one sulfur atom and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;
Z^1 represents halogen, -CN, $-A^2-C(O)R^{b2}$, $-A^2-C(O)N(R^{c2})R^{d2}$, $-A^2-C(O)OR^{e2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or heterocycloalkyl optionally substituted by =O;
Z^2 represents R^{a2}, $-C(O)OR^{e2}$ or =O;

A^2 represents a single bond or -N(H)-;

D^1 represents R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-SO_2N(R^{j4})R^{k4}$, $-SO_2OR^{l4}$, $-N(R^{n4})R^{o4}$, -N(H)CN, $-NO_2$, $-OR^{p4}$ or $-SR^{q4}$;

D^2 represents R^{a4}, $-A^4-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$, $-NO_2$, or $-OR^{p4}$;

Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$;

A^4 represents a single bond or -N(H)-;

each R^X and R^Y independently represent halogen, -CN, $-R^{a4}$ or $-OR^{p4}$;

R^{a4} represents C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, phenyl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

R^{c4} represents hydrogen, R^{a4} or $-C(O)OR^{e4}$;

each R^{b4} and R^{f4} independently represent C_{1-6}alkyl optionally substituted by one or more fluoro;

each, R^{d4}, R^{e4}, R^{j4}, R^{k4}, R^{l4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4} and R^{u4} independently represent hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, and/or R^{n4} and R^{o4} are linked together to form, along with the nitrogen atom to which they are attached, a 4- to 6-membered ring;

each G^1 independently represent one or more halogens;

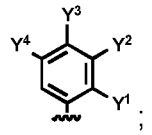
each G^3 and G^4 independently represent one or more more groups selected from halogen, R^{a5} or $-OR^{k5}$;

R^{a5} represents C_{1-6} alkyl optionally substituted by one or more fluoro;

R^{k5} represents hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; and

each n independently represents 1 or 2;

More particularly preferred compounds of formula I that may be mentioned include those in which R^1 represents



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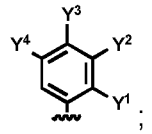
Y^3 and Y^4 represent hydrogen and Y^1 and Y^2 are selected from fluoro, chloro, -Me or $-CF_3$;

R^2 represents hydrogen;

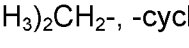
R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by one or more, preferably one to three, Z^1.

Examples of more particularly preferred compounds of formula I that may be mentioned are those where R^1 is 3-chloro-2-fluorophenyl, 2-chloro-3-methyl-phenyl, 3-chloro-2-methylphenyl, 2,3-dichlorophenyl, 2,3-dimethylphenyl or 2-methyl-3-trifluoromethyl;
R^2 represents hydrogen; and
R^3 represents -X-L-J or C_{1-6}alkyl optionally substituted by one to three, Z^1.

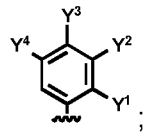
In some embodiments of the invention R^1 represents



;

at least one, preferably two, of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;
R^2 represents hydrogen;
R^3 represents -X-L-J;
X represents -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH_2C(CH_3)_2CH_2$-, -cyclopropylene- or  ;
L represents -L^1-L^2-;
L^1 represents -N(H)-, -O-, -C(O)N(H)-, -SO_2N(H)- or -N(H)C(O)N(H)-;
L^2 represents a single bond;
J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or a 5- to 10-membered monocyclic or bicyclic heteroaryl having 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by R^Y;

In some embodiments of the invention R^1 represents



;

at least one, preferably two, of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;
R^2 represents hydrogen;
R^3 represents -X-L-J;

X represents $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$ or -cyclopropylene-;

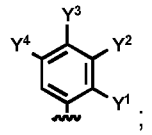
L represents $-L^1-L^2-$;

L^1 represents -N(H)-, -O-, -C(O)N(H)-, $-SO_2N(H)-$ or -N(H)C(O)N(H)-;

L^2 represents a single bond;

J represents phenyl optionally substituted by D^1 and optionally substituted by R^X, or a 5- to 10-membered monocyclic or bicyclic heteroaryl having either 1 to 3 nitrogen atoms, one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by R^Y;

In some embodiments of the invention R^1 represents



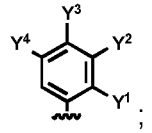
;

at least one, preferably two, of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

R^2 represents hydrogen;

R^3 represents $C_{1\text{-}6}$alkyl optionally substituted by one, two or three Z^1;

Preferred compounds that may be mentioned when R^1 represents

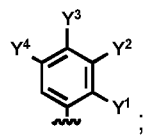


;

R^2 represents hydrogen; and

R^3 represents $C_{1\text{-}6}$alkyl substituted by one, two or three groups selected from Z^1 include those where Z^1 represents fluoro, bromo, -CN, $-C(O)NH_2$, $-C(O)NH_2$, -C(O)-(4-morpholinyl), -C(O)OMe, -C(O)OEt, -N(H)C(O)Me, $-N(H)C(O)CH_2NMe_2$, $-N(H)C(O)OCMe_3$, $-N(H)C(O)OCH_2Ph$, $-N(Me)C(O)OCMe_3$, -N(H)C(O)N(H)Me, $-N(H)C(O)N(H)CHMe_2$, -N(H)C(O)N(H)(4-morpholinyl), $-N(H)S(O)_2Me$, -OMe, $-OCF_3$, -OEt, $-OCH_2CH=CH_2$, $-OCH_2$cyclopropyl, 2-oxopyrrolidin-1-yl, 2-oxoimidazolidin-1-yl, 2-tetrahydrofuryl or 4-tetrahydropyranyl.

Preferred compounds that may be mentioned when R^1 represents



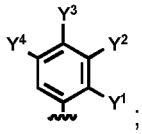
;

R^2 represents hydrogen;

R^3 represents C_{1-6}alkyl substituted by Z^1; and

Z^1 represents heterocycloalkyl, include those where Z^1 represents dihydropyridinyl, imidazolinyl, morpholinyl, piperidinyl, pyrrolidinyl, 2-tetrahydrofuryl or 4-tetrahydropyranyl, wherein the heterocycloalkyl is optionally substituted by -C(O)OC_{1-6}alkyl or =O.

In some embodiments of the invention R^1 represents



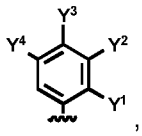
;

at least one, preferably two, of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

R^2 represents hydrogen or methyl; and

R^3 represents C_{1-10}alkyl.

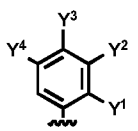
Preferred compounds that may be mentioned when R^1 represents



,

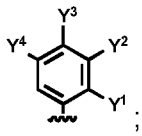
R^2 represents hydrogen and R^3 represents C_{1-10}alkyl, include those where R^3 represents -CH_3, -CD_3, ethyl, 1-propyl, 2-propyl, 1-butyl, *tert*-butyl, 3-pentyl, neopentyl, allyl, methallyl, 1-buten-4-yl, geranyl, propargyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, 2-cyclopropyl-2-ethyl, methylcyclopropyl, 2-(cyclohexen-1-yl)ethyl, bicyclo[2.2.1]hept-2-yl, 1-noradamantyl, 1-adamantyl or 3-pinanyl.

Preferred compounds that may be mentioned when R^1 represents



and R^2 represents methyl include those where R^3 represents cyclopropyl.

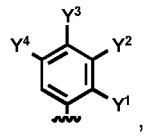
In some embodiments of the invention R^1 represents



;

at least two of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;
R^2 represents hydrogen; and
R^3 represents C_{2-10}alkyl.

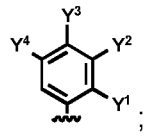
Preferred compounds that may be mentioned when R^1 represents



,

R^2 represents hydrogen and R^3 represents C_{2-10}alkyl, include those where R^3 represents ethyl, 1-propyl, 2-propyl, 1-butyl, *tert*-butyl, 3-pentyl, neopentyl, allyl, propargyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, 2-cyclopropyl-2-ethyl, methylcyclopropyl, bicyclo[2.2.1]hept-2-yl, 1-noradamantyl, 1-adamantyl or 3-pinanyl.

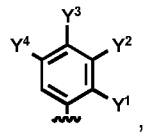
In some embodiments of the invention R^1 represents



;

at least two of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;
R^2 represents hydrogen; and
R^3 represents C_{3-10}alkyl, where the alkyl is cyclic or part cyclic.

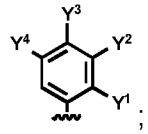
Preferred compounds that may be mentioned when R^1 represents



,

R^2 represents hydrogen and R^3 represents C_{3-10}alkyl, where the alkyl is cyclic or part cyclic include those where R^3 represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, 2-cyclopropyl-2-ethyl, methylcyclopropyl, 2-(cyclohexen-1-yl)ethyl, bicyclo[2.2.1]hept-2-yl, 1-noradamantyl, 1-adamantyl or 3-pinanyl.

In some embodiments of the invention R^1 represents



;

at least one, preferably two, of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

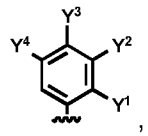
R^2 represents hydrogen;

R^3 represents heterocycloalkyl optionally substituted by one or two groups selected from Z^3;

Z^3 represents R^{a2} or -C(O)OR^{e2}; and

R^{a2} and R^{e2} represents C_{1-4}alkyl.

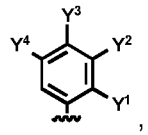
Preferred compounds that may be mentioned when R^1 represents



,

R^2 represents hydrogen and R^3 represents heterocycloalkyl optionally substituted by one or two groups selected from Z^3, include those where R^3 represents tetrahydrofuranyl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl or quinuclidinyl.

Particularly preferred compounds that may be mentioned when R^1 represents



,

R^2 represents hydrogen and R^3 represents heterocycloalkyl optionally substituted by one or two gropups selected from Z^3, include those where R^3 represents tetrahydrofuran-3-yl, tetrahydropyran-4-yl, 2,2-dimethyltetrahydropyran-4-yl, 1-(*tert*-butoxycarbonyl)azetidin-3-yl, 1-(*tert*-butoxycarbonyl)-piperidin-4-yl, 1-(ethoxycarbonyl)-piperidin-4-yl or quinuclidin-3-yl.

In some embodiments R^1 is a 6-membered heteroaryl substituted by one or more groups selected from Y^5. Such a 6-membered heteroaryl e.g. may be pyridyl, pyrimidinyl or pyrazinyl.

In some embodiments of the invention, R^1 represents (ii) a 6-membered heteroaryl substituted by one or more groups Y^5, wherein each Y^5 is as defined herein above.

In some particular embodiments, when R^1 represents a 6-membered heteroaryl, it is substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

Preferred compounds of formula I that may be mentioned when R^1 represents a 6-membered heteroaryl include those in which R^1 represents pyridyl, preferably 3- or 4-pyridinyl, substituted by one or more Y^5;
R^2 represents hydrogen;
R^3 represents C_{1-6}alkyl;
Y^5 represents halogen, R^a, -OH or -OR^m; and
R^a and R^m represents C_{1-6}alkyl optionally substituted by -OH or one or more fluoro.

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a 6-membered heteroaryl include those in which R^1 represents 3-pyridinyl substituted in the 6-position by -CH_2OH or -OH, or in the 2-position by -CF_3, or 4-pyridinyl substituted in the 3-position by chloro and optionally in the 2-position by -OCH_3;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl.

In some embodiments of the invention R^1 represents a 6-membered heteroaryl substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl optionally substituted by one or more Z^1.

In some embodiments, R^1 represents a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine of formula I via a carbon atom of the

heteroaryl ring, which heteroaryl ring is optionally substituted by one or more groups selected from Y^5, wherein each Y^5 is as defined herein above.

In some embodiments, R^1 represents a 5- to 7-membered monocyclic heteroaryl, e.g. a 5- or 6-membered heteroaryl, in particular a 5-membered heteroaryl, connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, wherein each Y^5 is as defined herein above.

In some particular embodiments, when R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, said heteroaryl optionally being substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by Z^1;

Preferred compounds of formula I that may be mentioned when R^1 represents a 5-membered heteroaryl connected to the ring of the compound pyrimidine of formula I via a carbon atom of the heteroaryl ring, include those in which R^1 represents oxazolyl, pyrazolyl, thiazolyl, or preferably, furanyl, isoxazyl, pyrrolyl or thiophenyl, which heteroaryl rings are optionally substituted by one or more groups selected from Y^5;
R^2 represents hydrogen;
R^3 represents -X-L-J;
Y^5 represents R^a, -C(O)R^b, -SO_2R^f or -$SO_2N(R^i)R^j$;
X represents C_{1-6}alkylene-, e.g. -CH_2CH_2-;
L represents -L^1-L^2-, or preferably, a single bond;
L^1 represents -N(H)-;
L^2 represents a single bond;
J represents phenyl optionally substituted in the 3-position, but preferably in the 4-position, by D^1 and optionally substituted by one or more groups selected from R^X;
D^1 represents -C(O)N(R^{c4})R^{d4}, or preferably, -SO_2R^{f4}, or -$SO_2N(R^{j4})R^{k4}$;
each R^X independently represent R^{a4}, or preferably, halogen;
R^a represents C_{1-6}alkyl, preferably C_1alkyl optionally substituted by one or more fluoro, but preferably C_{1-6}alkyl substituted by -N(H)C(O)OR^{e1};

each R^b and R^f independently represent C_{1-6}alkyl;
each R^i and R^j independently represent hydrogen or C_{1-4}alkyl;
R^{e1} represents C_{1-6}alkyl;
each R^{a4} and R^{f4} represents C_{1-4}alkyl optionally substituted by one or more fluoro (but are preferably unsubstituted); and
each R^{c4}, R^{d4}, R^{j4} and R^{k4} independently represents hydrogen or C_{1-4}alkyl optionally substituted by one or more fluoro (but preferably unsubstituted).

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents furanyl, isoxazyl, pyrrolyl or thiophenyl which heteroaryls are optionally substituted by one or more groups selected from halogen, $-CH_3$, $-C(O)CH_3$, $-CH_2N(H)C(O)OC(CH_3)_3$ or $-SO_2N(H)C(CH_3)_3$;
R^2 represents hydrogen;
R^3 represents $-CH_2CH_2$-J; and
J represents phenyl substituted in the 4-position by chloro, $-SO_2CH_3$ or $-SO_2NH_2$.

In some embodiments of the invention R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more Y^5;
R^2 represents hydrogen;
R^3 represents -X-L-J.

Other preferred compounds of formula I that may be mentioned when R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents isoxazyl, oxazolyl, thiazolyl, or preferably, furanyl, pyrazolyl, pyrrolyl or thiophenyl, which heteroaryl rings are optionally substituted by one or more groups selected from Y^5;
R^2 represents hydrogen;
R^3 represents C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1;
Y^5 represents halogen, or preferably R^a;
Z^1 represents heterocycloalkyl, optionally substituted by =O;

R^a represents C_{1-6}alkyl optionally substituted by one or more fluoro, but preferably C_{1-6}alkyl substituted by $-C(O)N(R^{c1})R^{d1}$ or $-N(R^{h1})R^{i1}$;
each R^{c1}, R^{d1}, R^{h1} and R^{i1} independently represents hydrogen or C_{1-4}alkyl, but preferably all represent hydrogen; or
R^{h1} and R^{i1} are linked together to form, along with the nitrogen atom to which they are attached, a 6-, or preferably, a 5-membered ring.

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents furanyl, pyrazolyl, pyrrolyl or thiophenyl, which heteroaryl rings are optionally substituted by $-CH_3$, $-CH_2CH_2C(O)NH_2$ or $-CH_2$-(1-pyrrolidinyl);
R^2 represents hydrogen;
R^3 represents C_{2-4}alkyl optionally substituted by Z^1;
Z^1 represents pyrrolidinyl substituted by =O, preferably 2-oxopyrrolidin-1-yl.

In some embodiments of the invention R^1 represents a 5-membered heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more one or more groups selected from Y^5;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

In some embodiments, R^1 represents a 8- to 10-membered bicyclic heteroaryl, e.g. a 9- to 10-membered heteroaryl, connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, wherein each Y^5 is as defined herein above.

In some particular embodiments, when R^1 represents such a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, said heteroaryl is optionally substituted by one or more groups selected from Y^5;
R^2 represents hydrogen; and

R^3 represents -X-L-J or C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

Preferred compounds of formula I that may be mentioned when R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl ring, include those in which R^1 represents benzofuranyl, indazolyl, or preferably, benzothiophenyl, indolyl and quinolinyl which heteroaryls are optionally substituted by one or more groups selected from Y^5;

R^2 represents hydrogen;

R^3 represents -X-L-J;

each Y^5 independently represent halogen, or preferably, R^a;

X represents -C_{1-6}alkylene-, e.g. -CH_2CH_2-;

L represents -L^1-L^2- or preferably, a single bond;

L^1 represents -O-, -N(H)-;

L^2 represents a single bond;

J represents phenyl optionally substituted in the 3-position, but preferably in the 4-position, by D^1 and optionally substituted by one group selected from R^X;

D^1 represents -C(O)N(R^{c4})R^{d4} or -SO_2R^{f4}, or preferably, -SO_2N(R^{j4})R^{k4};

R^X represents R^{a4}, or preferably, halogen;

each R^{a4} and R^{f4} represents C_{1-4}alkyl optionally substituted by one or more fluoro (but preferably unsubstituted); and

each R^{c4}, R^{d4}, R^{j4} and R^{k4} independently represents hydrogen or C_{1-4}alkyl optionally substituted by one or more fluoro (but preferably unsubstituted).

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents 3-benzothiophenyl, 4-indolyl or 5-quinolinyl, all optionally substituted by one or more chloro, fluoro, -CH_3 or -CF_3, but preferably unsubstituted;

R^2 represents hydrogen;

R^3 represents -CH_2CH_2-J; and

J represents phenyl optionally substituted in the 4-position by fluoro or -SO_2CH_3, or preferably by, chloro or-SO_2NH_2.

In some embodiments of the invention R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents -X-L-J.

Other preferred compounds of formula I that may be mentioned when R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents 7-azaindolyl, benzofuranyl, benzothiophenyl, 2,3-dihydrobenzofuranyl, indazolyl, indolyl, isoquinolinyl, quinolinyl, and which heteroaryls are optionally substituted by one or more groups selected from Y^5;
R^2 represents hydrogen;
R^3 represents C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1;
each Y^5 independently represent halogen, or preferably, R^a or $-SO_2R^f$;
Z^1 represents heterocycloalkyl, optionally substituted by =O;
R^a represents C_{1-6}alkyl optionally substituted by one or more fluoro; and
R^f represents phenyl optionally substituted by halogen or C_{1-4}alkyl optionally substituted by one or more fluoro;

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, include those in which R^1 represents 7-azaindol-3-yl, benzofuran-3-yl, benzothiophen-3-yl, 2,3-dihydrobenzofuran-7-yl, indazol-5-yl, indazol-6-yl, indol-3-yl, indol-4-yl, indol-5-yl, isoquinolin-4-yl, quinolin-5-yl, and which heteroaryls are optionally substituted by one or more groups selected from Y^5;
R^2 represents hydrogen;
R^3 represents C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1;
each Y^5 independently represent fluoro, chloro, or preferably, R^a or $-SO_2R^f$;
Z^1 represents pyrrolidinyl substituted by =O, preferably 2-oxopyrrolidin-1-yl;
R^a represents $-CF_3$, or preferably, $-CH_3$;

R^f represents phenyl optionally substituted in the 4-position by fluoro, or preferably by, chloro, $-CH_3$ or $-CF_3$; and
each Z^1 independently represents pyrrolidinyl substituted by =O, preferably 2-oxopyrrolidin-1-yl.

In some embodiments of the invention R^1 represents a bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl ring, which ring is optionally substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl optionally substituted by Z^1.

In certain embodiments of the invention R^1 represents indolyl, e.g. indol-3-yl, indol-4-yl or indol-5-yl, where the indolyls are optionally substituted in the 1-position by Y^5;
R^2 represents hydrogen;
R^3 represents C_{1-6}alkyl;
Y^5 represents $-SO_2R^f$; and
R^f represents phenyl optionally substituted in the 4-position by chloro, $-CH_3$ or $-CF_3$.

In some embodiments of the invention, R^1 represents (iv) -ethynyl-Y^6, wherein Y^6 is as defined herein above.

In some particular embodiments, when R^1 represents -ethynyl-Y^6, Y^6 in particular may represent phenyl optionally substituted by halogen or C_{1-6}alkyl optionally substituted by one or more halogens;
R^2 represents hydrogen; and
R^3 represents C_{1-6}alkyl optionally substituted by Z^1.

Preferred compounds of formula I that may be mentioned when R^1 represents ethynyl-Y^6 include those where Y^6 represents phenyl optionally substituted by one or more halogens and/or C_{1-6}alkyl optionally substituted by one or mote halogens;
R^2 represents hydrogen; and
R^3 represents-C_{1-6}alkyl.

In some embodiments of the invention R^1 represents ethynyl-Y^6;
R^2 represents hydrogen; and
R^3 represents -X-L-J, or preferably, C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1;

In some embodiments, R^1 represents a 3- to 8-membered nonaromatic ring, in particular a 5- to 7-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7.

In some particular embodiments, when R^1 represents a 3- to 8-membered nonaromatic ring, R^1 optionally contains one or two heteroatoms, optionally contains one or two double bonds and is optionally substituted by one or more groups selected from Y^7;
R^2 represents hydrogen; and
R^3 represents -X-L-J.

Preferred compounds of formula I that may be mentioned when R^1 represents a nonaromatic ring include those where R^1 is 5-7 membered nonaromatic ring optionally containing one heteroatom and/or one double bond and is optionally substituted by one or more groups selected from Y^7;
R^2 represents hydrogen;
R^3 represents -X-L-J;
each Y^7 independently represents R^a, $-C(O)R^b$, $-C(O)OR^e$ or $-SO_2R^f$;
X represents -C_{1-6}alkylene-, e.g. $-CH_2CH_2-$;
L represents $-L^1-L^2-$, or preferably, a single bond;
L^1 represents -N(H)- or -O-;
L^2 represents a single bond;
J represents phenyl optionally substituted in the 3-position, but preferably in the 4-position, by D^1;
D^1 represents $-C(O)N(R^{c4})R^{d4}$, or preferably, $-SO_2R^{f4}$ or $-SO_2N(R^{j4})R^{k4}$;
each R^a and R^e independently represent C_{1-6}alkyl optionally substituted by one or more fluoro;
each R^b and R^f independently represent C_{1-6}alkyl optionally substituted by one or more fluoro, phenyl optionally substituted by one or more halogens and/or by one

or more more R^{a1}, or heteroaryl optionally substituted by one or more halogens and/or by one or more R^{a1};
each R^{a1} independently represent C_{1-6}alkyl optionally substituted by one or more fluoro;
each R^{c4}, R^{d4}, R^{j4} and R^{k4} independently represent hydrogen or C_{1-4}alkyl optionally substituted by one or more fluoro (but preferably unsubstituted); and
R^{f4} represents C_{1-4}alkyl optionally substituted by one or more fluoro (but preferably unsubstituted).

Particularly preferred compounds of formula I that may be mentioned when R^1 represents a nonaromatic ring include those where R^1 is 5-7 membered and optionally contains one heteroatom and/or one double bond and is optionally substituted by one or more groups selected from Y^7;
R^2 represents hydrogen;
R^3 represents $-CH_2CH_2$-J;
Y^7 represents $-C(O)R^b$, $-C(O)OR^e$ or $-SO_2R^f$;
J represents phenyl substituted in the 4-position by $-SO_2Me$ or $-SO_2NH_2$;
each R^e independently represent C_{1-6}alkyl;
each R^b and R^f independently represent C_{1-6}alkyl, phenyl optionally substituted by R^{a1} or heteroaryl optionally substituted by R^{a1}; and
each R^{a1} independently represent C_{1-6}alkyl.

More particularly preferred compounds of formula I that may be mentioned when R^1 represents a nonaromatic ring include those where R^1 represents cycloheptanyl, cyclohexanyl, cyclopentanyl, piperidin-3-yl, pyrrolidin-3-yl, or preferably, cyclohepten-1-yl, piperidin-4-yl or 1,2,3,6-tetrahydropiperidin-4-yl and where the piperidine, pyrrolidine and the 1,2,3,6-tetrahydropiperidin-4-yl are preferably substituted in the 1-position by -C(O)Me, $-C(O)CH(CH_3)_2$, -C(O)cyclopentyl, -C(O)methylcyclopentyl, -C(O)(4-methylphenyl), -C(O)(5-isoxazolyl), $-C(O)OC(CH_3)_3$, $-SO_2Me$ or $-SO_2$(4-methylphenyl).

In some embodiments of the invention R^1 represents a 3-8 membered nonaromatic ring optionally substituted by one or more groups selected from Y^7;
R^2 represents hydrogen; and
R^3 represents -X-L-J;

When R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, the link formed by R^2 and R^3 is optionally substituted by one or more Z^3 and optionally substituted by -X-L-J.

Preferred compounds of formula I that may be mentioned when R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring are those wherein the link formed by R^2 and R^3 is optionally substituted by one or more C_{1-6}alkyl or =O, but wherein the link is preferably unsubstituted or substituted by methyl.

In some embodiments of the invention R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more Z^3 and optionally substituted by -X-L-J;

In a compound of formula I, the moiety X represents -C_{1-6}alkylene-, optionally substituted by one or more T^1, or -$(C(R^A)_2)_p$-C_{2-5}heterocycloalkylene-$(C(R^A)_2)_q$-, where the heterocycloalkylene is optionally substituted by one or more T^2.

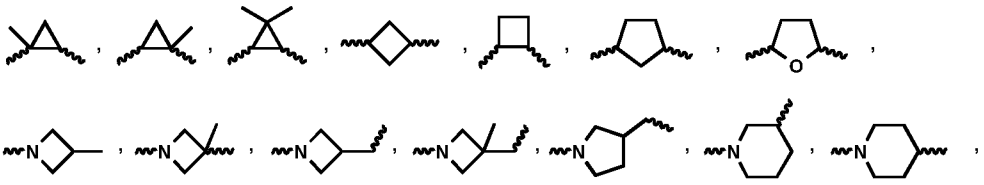
In some embodiments, X represents -C_{1-6}alkylene-, optionally substituted by one or more T^1.

In some embodiments, X represents -C_{2-4}alkylene-substituted by T^1;
T^1 represents -OR^{d3}, and
R^{d3} represents C_{1-4}alkyl, or preferably, hydrogen.

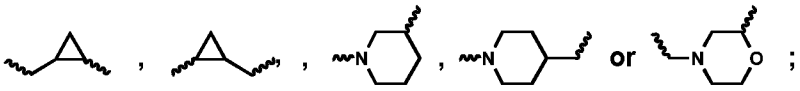
Particular compounds of formula I that may be mentioned include those in which X represents -$CH_2CH(OH)$-.

In some other embodiments, X represents -$(C(R^A)_2)_p$-C_{2-5}heterocycloalkylene-$(C(R^A)_2)_q$-, where the heterocycloalkylene is optionally substituted by one or more T^2.

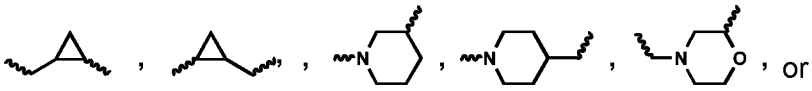
When R^1 is phenyl, heteroaryl, -ethynyl-Y^6 or a 3- to 8-membered nonaromatic ring and R^2 is hydrogen and R^3 represents -X-L-J; or
when R^2 and R^3 are linked together, and the link formed between R^2 and R^3 is substituted by -X-L-J, then X preferably represents



or more preferably, $-CH_2-$, $-CH_2CH_2-$, -CH(Me)-, $-C(Me)_2-$, $-CH_2CH(Me)-$, $-CH(Me)CH_2-$, $-CH_2CH_2CH_2-$, $-CH(Me)CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, -cyclopropylene-, $-CH_2-C\equiv C-CH_2-$,



Preferred compounds of formula I that may be mentioned include those where X represents -CH(Me)-, $-C(Me)_2-$, $-CH_2CH(Me)-$, $-CH(Me)CH_2-$, $-CH(Me)CH_2CH_2-$,



preferably $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, -cyclopropylene-, $-CH_2-C\equiv C-CH_2-$, or more preferably, $-CH_2CH_2-$.

In some embodiments L represents a single bond.

In some embodiments L represents $-L^1-L^2-$.

Compounds of formula I that may be mentioned include those where L^1 represents $-N(R^B)-$, -O-, $-S(O)_m-$, $-C(O)N(R^C)-$, $-N(R^D)C(O)-$, $-S(O)_nN(R^E)-$, $-N(R^F)S(O)_n-$ or $-N(R^G)C(O)N(R^H)-$.

Preferred compounds of formula I that may be mentioned include those where L^1 represents $-N(R^B)-$, -O-, $-S(O)_m-$, $-C(O)N(R^C)-$, $-S(O)_nN(R^E)-$, or $-N(R^G)C(O)N(R^H)-$.

Particularly preferred compounds of formula I that may be mentioned include those where L^1 represents -N(H)-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(O)N(H)-, -$S(O)_n$N(H)- or -N(H)C(O)N(H)-;

Compounds of formula I that may be mentioned include those in which L^2 represents a single bond or -C_{1-2}alkylene-.

In some embodiments, L^2 represents a single bond.

In some embodiments, L^2 represents -C_{1-2}alkylene-, i.e. -CH_2- and -CH_2CH_2-.

In a compound of formula (I), J represents

(i) a 6- to 10-membered aryl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or

(ii) a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which heteroaryl is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

In some embodiments, J represents (i) a 6- to 10-membered aryl, e.g. phenyl, said aryl optionally being substituted by D^1 and optionally being substituted by one or more groups selected from R^X.

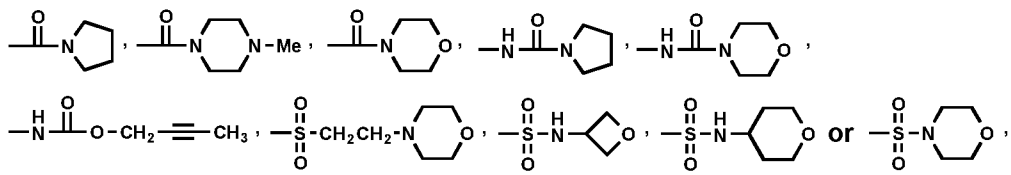
In some other embodiments, J represents (ii) a 5- to 11-membered monocyclic or bicyclic heteroaryl, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

In some particular embodiments, J represents (ii) a 5- to 7-membered, e.g. 5- or 6-membered, monocyclic heteroaryl, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

In some other particular embodiments, J represents (ii) a 8- to 11-membered, in particular 9- or 10-membered, bicyclic heteroaryl, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

Compounds of formula I that may be mentioned include those in which J represents phenyl substituted by halogen, $-B(OH)_2$, -CN, R^{a4}, $-C(Q^2)R^{b4}$, $-N(H)C(O)R^{b4}$, $-C(Q^2)N(H)R^{d4}$, $-N(H)C(O)N(H)R^{d4}$, $-N(H)C(NR^w)N(H)R^{d4}$, $-C(O)OR^{e4}$, $-N(H)C(O)OR^{e4}$, $-C(O)N(H)S(O)_2R^{f4}$, $-N(H)S(O)_nR^{f4}$, $-S(O)_nR^{f4}$, $-S(NR^{h4})(O)R^{i4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$, $-NO_2$, $-OR^{p4}$, $-S(O)_2OH$, $-SR^t$ or a 5-membered heteroaryl.

Preferred compounds of formula I that may be mentioned include those in which J represents phenyl substituted, preferably in the 3- or 4-position, by fluoro, chloro, bromo, $-B(OH)_2$, methyl, ethyl, ethynyl, $-CF_3$, -CN, -C(O)Me, $-C(O)NH_2$, $-C(NH)NH_2$, $-C(NOH)NH_2$, $-C(S)NH_2$, -C(O)N(H)Me, $-C(O)NHCH(CH_3)CH_2OH$, $-C(O)N(CH_3)$propargyl, $-C(O)N(H)NH_2$, -C(O)N(H)OH, $-C(O)N(H)S(O)_2Me$, -C(O)OH, -CO(O)Me, -C(O)OEt, $-C(O)OCH_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)OCH_2CH_2OH$, $-C(O)OCH_2CH_2SO_2Me$, $-C(O)OCH_2CH(OH)CH_2OH$, $-NH_2$, $-NMe_2$, -N(H)CN, $-N(H)C(NH)NH_2$, -NHC(O)Me, -NH(CO)cyclopropyl, $-NH(CO)C(Me)_3$, -NHC(O)OEt, $-NHC(O)OCH(Me)_2$, $-NHC(O)OC(Me)_3$, $-NHC(O)OCH_2CH(Me)_2$, $-NHC(O)OCH_2C(Me)_3$, $-NHC(O)OCH_2CH_2OMe$, -N(H)C(O)N(H)Et, $-N(H)C(O)N(H)CH(Me)_2$, $-N(H)C(O)N(H)C(Me)_3$, $-N(H)C(O)N(H)CH(Me)CH_2CH_3$,$-N(H)C(O)N(H)CH_2CH=CH_2$, $-N(H)C(O)N(CH_3)_2$, -N(H)C(O)N(H)C(O)OEt, -N(H)C(S)N(H)Et, $-NO_2$, $-NHS(O)_2Me$, $-NHS(O)_2Et$, $-NHS(O)_2CH(Me)_2$, $-NHS(O)_2CH_2CH(Me)_2$, $-NHS(O)_2CH_2CF_3$, -OH, -OMe, -SMe, -S(O)Me, -S(NH)(O)Me, $-S(O)_2Me$, $-S(O)_2CF_3$, $-S(O)_2CH(CH_3)_2$, $-S(O)_2CH_2CH_2N(Me)_2$,$-S(O)_2CH_2CH_2CH_2NMe_2$, $-S(O)NH_2$, $-S(O)_2NH_2$, $-S(O)_2NHMe$, $-S(O)_2NHCH_2CH_2OMe$, $-S(O)_2OH$,

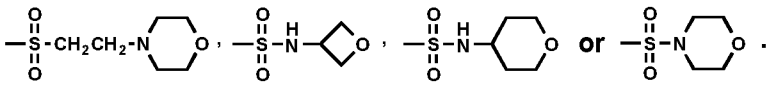


2-imidazolyl, 1,3,4-oxadiazol-2-yl, 2-oxazolyl, 5-tetrazolyl, 2-thiazolyl and optionally substituted by one or more (e.g. two, or more preferably one) fluoro, chloro, -Me, -OH, -OMe or $-CF_3$.

Examples of particularly preferred compounds of formula I that may be mentioned include those in which J represents phenyl substituted in the 3- or 4-position by $-C(O)NH_2$, -C(O)N(H)Me, -C(O)OEt, -NHC(O)Me, -NH(CO)cyclopropyl, $-NH(CO)C(Me)_3$, $-NHS(O)_2Me$, $-NHS(O)_2Et$, $-NHS(O)_2CH(Me)_2$, $-NHS(O)_2CH_2CF_3$, $-S(O)_2Me$, $-S(O)_2NH_2$ or $-S(O)_2NHMe$.

Examples of particularly preferred compounds of formula I that may be mentioned include those in which J represents phenyl substituted, preferably in the 4-position, by $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-C(O)OCH_2CH_2CH_3$, $-C(O)OCH_2CH(CH_3)_2$, $-C(O)OCH_2CH_2OH$, $-C(O)OCH_2CH_2SO_2Me$ and $-C(O)OCH_2CH(OH)CH_2OH$.

Examples of particularly preferred compounds of formula I that may be mentioned include those in which J represents phenyl substituted, preferably in the 4-position, by $-SO_2CH(CH_3)_2$, $-SO_2NHCH_2CH_2OMe$,



Compounds of formula I that may be mentioned include those in which J represents heteroaryl optionally substituted by halogen, $-B(OR^{m4})_2$, -CN, R^{a4}, $-C(Q^2)R^{b4}$, $-N(H)C(O)R^{b4}$, $-C(Q^2)N(H)R^{d4}$, $-N(H)C(O)N(H)R^{d4}$, $-N(H)C(NR^w)N(H)R^{d4}$, $-C(O)OR^{e4}$, $-N(H)C(O)OR^{e4}$, $-C(O)N(H)S(O)_2R^{f4}$, $-N(H)S(O)_nR^{f4}$, $-S(O)_nR^{f4}$, $-S(NR^{h4})(O)R^{i4}$, $-S(O)_nN(R^{j4})R^{k4}$, $-N(R^{n4})R^{o4}$, $-NO_2$, $-OR^{p4}$, $-S(O)_2OH$, $-SR^t$, phenyl optionally substituted by halogen, or pyridinyl optionally substituted by halogen.

In some embodiments, when J is a heteroaryl as defined herein above, said heteroaryl is 6-membered. Particular compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents pyridinyl optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

D^2 represents halogen, R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nC(O)R^{g4}$, $-A^4-S(NR^{h4})(O)R^{i4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-A^4-S(O)_nOR^{l4}$, $-B(OR^{m4})_2$, $-N(R^{n4})R^{o4}$, $-NO_2$ or $-OR^{p4}$;
Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$; and
R^Y represents halogen or C_{1-3} alkyl optionally substituted by one or more fluoro.

Preferred compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 4-pyridinyl, or preferably, 2-pyridinyl or 3-pyridinyl optionally substituted by R^{a4}, $-C(Q^2)N(H)R^{d4}$, $-C(O)OR^{e4}$, $-N(H)C(O)R^{b4}$, $-B(OR^{m4})_2$, $-NO_2$, $-N(H)S(O)_nR^{f4}$, $-S(O)_nR^{f4}$, $-N(R^{n4})R^{o4}$ or $-OR^{p4}$.

Particular compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 2-pyridinyl substituted in the 4-position by $-C(O)NH_2$, -C(O)OMe or in the 5-position by $-CF_3$, $-C(O)NH_2$, -C(O)OH, -C(O)OEt, -N(H)C(O)Me, $-N(H)C(O)N(H)C(CH_3)_3$, $-N(H)C(O)OC(CH_3)_3$, $-N(H)SO_2Me$, $-NO_2$, $-SO_2Me$, $-SO_2NH_2$ or $-SO_2N(H)Me$, 3-pyridinyl substituted in the 4-position by $-NH_2$ or $-SO_2Me$, or pyridinyl substituted in the 4-position by -OMe and in the 5-position by Me, or substituted in the 5-position by $-SO_2NH_2$.

Particular compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents pyrimidinyl optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;
D^2 represents $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-A^4-S(O)_nOR^{l4}$, $-B(OR^{m4})_2$, or $-N(R^{n4})R^{o4}$;
Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$; and
R^Y represents halogen or C_{1-3} alkyl optionally substituted by one or more fluoro.

Preferred compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 2-pyrimidinyl or 4-pyrimidinyl substituted by $-N(H)C(O)R^{b4}$, $-C(O)N(H)R^{d4}$, $-C(O)OR^{e4}$, $-N(H)S(O)_nR^{f4}$, $-S(O)_nR^{f4}$, or $-N(R^{n4})R^{o4}$.

Particularly preferred compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 2-pyrimidinyl substituted in the 4-position by $-C(O)NH_2$, -C(O)OH, -C(O)OMe, $-NH_2$, $-S(O)_2Me$ or $-S(O)_2NH_2$, substituted in the 5-position by $-C(O)NH_2$, or 4-pyrimidinyl substituted in the 2-position by $-C(O)NH_2$, $-NH_2$, $-S(O)_2Me$ or $-S(O)_2NH_2$; and
R^2 represents halogen (e.g. fluoro or chloro), or preferably, $-CF_3$.

For example, particularly preferred compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 2-pyrimidinyl substituted in the 4-position by $-S(O)_2Me$ or $-S(O)_2NH_2$, or preferably by $-C(O)NH_2$ or -C(O)OMe.

Particular compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents pyrazinyl optionally substituted by D^2;
D^2 represents $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-A^4-S(O)_nOR^{l4}$, $-B(OR^{m4})_2$ or $-N(R^{n4})R^{o4}$; and
Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$.

Preferred compounds of formula I that may be mentioned when J represents a 6-membered heteroaryl include those in which J represents 2-pyrazinyl substituted in the 6-position, or preferably in the 3- or 5-position by $-S(O)_2Me$ or $-S(O)_2NH_2$, or preferably, by $-C(O)NH_2$ or -C(O)OMe.

In some embodiments of the invention J represents 1,3,5-triazinyl substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

In some embodiments, when J represents a 6-membered heteroaryl, in particular 1,3,5-triazinyl, substituted by D^2 and optionally substituted by one or more groups selected from R^2,
D^2 in particular may represent $-A-C(O)R^c$, $-A-C(O)N(R^d)R^e$, $-A-C(O)OR^f$, $-A-S(O)_nR^g$, $-A-S(O)_nN(R^k)R^l$, or $-N(R^o)R^p$.

Particularly preferred compounds of formula I that may be mentioned include those in which J represents 1,3,5-triazinyl substituted by $-C(O)NH_2$, $-C(O)OR^f$, $-S(O)_2R^g$, $-S(O)_2NH_2$, or in particular one or two $-NH_2$.

In some embodiments, when J is a heteroaryl as defined herein above, said heteroaryl is 5-membered. Particular compounds of formula I that may be mentioned when J represents heteroaryl include those in which J represents a 5-membered heteroaryl optionally substituted by D^2;
D^2 represents $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$, $-B(OR^{m4})_2$ or $-N(R^{n4})R^{o4}$; and
Q^2 represents =O, =S, $=NR^{r4}$ or $=N(OR^{u4})$.

Preferred compounds of formula I that may be mentioned when J represents a 5-membered heteroaryl include those in which J represents furanyl, imidazolyl, isoxazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyrazolyl, 1,3,4-thiadiazolyl, thiazolyl, 1,2,3-triazolyl or thiophenyl, optionally substituted by halogen, $-CH_3$, cyclopropyl, $-C(O)NH_2$, -C(O)OMe, $-NH_2$, $-S(O)_2Me$ or $-S(O)_2NH_2$.

Particular compounds of formula I that may be mentioned include those in which J represents a bicyclic heteroaryl optionally substituted by D^2, and optionally substituted by one or more groups selected from R^Y;
D^2 represents R^{a4}, $-A^4-C(Q^2)R^{b4}$, $-A^4-C(Q^2)N(R^{c4})R^{d4}$, $-A^4-C(Q^2)OR^{e4}$, $-A^4-S(O)_nR^{f4}$, $-A^4-S(O)_nN(R^{j4})R^{k4}$ or $-N(R^{n4})R^{o4}$; and
each R^Y independently represent halogen, -CN, C_{1-3} alkyl optionally substituted by F or $-OC_{1-3}$ alkyl optionally substituted by fluoro, or, when Y is partly aromatic, =O.

Certain compounds of formula I where J represents a bicyclic heteroaryl that may be mentioned include those where the bicyclic heteroaryl is connected to L via a 5-membered ring and where the bicyclic heteroaryl is optionally substituted by D^2 and optionally substituted by one or more substituents independently selected from R^Y.

Certain compounds of formula I where J represents a bicyclic heteroaryl that may be mentioned include those where the bicyclic heteroaryl is connected to L via a

6-membered ring and where the bicyclic heteroaryl is optionally substituted by D^2 and optionally substituted by one or more substituents independently selected from R^Y.

Preferred compounds of formula I that may be mentioned when J represents a bicyclic heteroaryl include those where J represents benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiophenyl, 2,3-dihydrobenz[1,3]oxazin-6-yl, 3,4-dihydrobenz[1,4]oxazinyl, dihydrobenzothiophenyl, furo[2,3-*c*]pyridin-5-yl, imidazo[1,2-*a*]pyridinyl, indolyl, isoindolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinazolinyl, thieno[3,2-*b*]thiophenyl, thiochromanyl, quinolinyl, quinazolinyl, or purin-6-yl, all optionally substituted by one or more groups selected from fluoro, chloro, -Me, $-CHF_2$, $-CF_3$, $-NH_2$, -NHMe, $-NMe_2$, -OH, -OMe, =NH or =O.

Particularly preferred compounds of formula I that may be mentioned when J represents a bicyclic heteroaryl, L^2 is a single bond and L^1 is -N(H)- include those where J represents imidazo[2,1-*b*]thiazol-6-yl, 1,1-dioxobenzothiophen-6-yl, 1-oxo-1-iminobenzothiophen-6-yl, thieno[3,2-*b*]thiophen-2-yl or more preferably, 2-methyl-1,3-benzothiazol-5-yl, 2-methyl-1,3-benzothiazol-6-yl, 4-oxo-quinazolin-7-yl, 3,4-dihydro-3-oxo-1,4-benzoxazin-6-yl, 3,4-dihydro-4-methyl-3-oxo-1,4-benzoxazin-6-yl, 3,4-dihydro-2,2-dimethyl-3-oxo-1,4-benzoxazin-6-yl, purin-6-yl, 2-aminopurin-6-yl.

In one embodiment, the compound according to the invention is selected from the compounds of Examples 1-761.

As discussed hereinbefore, compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore defined, for use as a pharmaceutical.

In another aspect of the invention the use of a compound of the invention, as hereinbefore defined, is provided for the manufacture of a medicament for the treatment of autoimmune or inflammatory conditions.

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

By "prodrug of a compound of the invention", we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time, following enteral or parenteral administration (e.g. oral or parenteral administration). All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds, which possess pharmacological activity.

It is stated herein that the compounds of the invention may be useful in the treatment of autoimmune or inflammatory conditions. For the purposes of this specification, and for the avoidance of doubt, the term "treatment" includes treatment *per se*, prevention and prophylaxis.

Preferably the autoimmune or inflammatory conditions are selected from the group comprising: rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

In certain embodiments of the present invention, the autoimmune or inflammatory conditions are selected from rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis, rejection after organ transplantation, psoriasis and atherosclerosis.

In certain embodiments of the present invention, the autoimmune or inflammatory conditions are selected from rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis, rejection after organ transplantation, and atherosclerosis.

In certain embodiments of the present invention, the autoimmune or inflammatory condition is not psoriasis.

Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, intranasally, topically, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical compositions/formulations, including tablets, capsules or elixirs for oral administration, suppositories for

rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Compounds of the invention (i.e. compounds that inhibit MTH1) may be administered in the form of tablets or capsules, e.g., time-release capsules that are taken orally. Alternatively, the compounds of the invention may be in a liquid form and may be taken orally or by injection. The compounds of the invention may also be in the form of suppositories, or, creams, gels, and foams e.g. that can be applied to the skin. In addition, they may be in the form of an inhalant that is applied nasally.

Such compositions/formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical composition/formulation including a compound of the invention, as hereinbefore defined, optionally in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier. Such compositions/formulations may be of use in the treatment, prevention and/or prophylaxis of autoimmune and inflammatory conditions which benefit by inhibition of MTH1.

Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

The invention further provides a process for the preparation of a pharmaceutical formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In yet another aspect the present invention provides methods for the treatment of autoimmune and inflammatory conditions comprising administering a therapeutically effective amount of a compound of the invention to a subject (e.g. patient) in need of such treatment.

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of autoimmune and inflammatory conditions.

Examples of therapeutic agents that may be useful in combination with compounds of this invention are glucocorticoids (e.g. cortisone or prednisolone, TNF-alpha inhibitors (e.g. infliximab), anti-CD20 (e.g. rituximab), immunosupressants (e.g. mycophenolate mofetil or azathioprine) or antimetabolites (e.g. methotrexate).

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined; and

(B) another therapeutic agent that is useful in the treatment of an autoimmune or inflammatory condition,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined

preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of autoimmune diseases and inflammatory conditions, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of autoimmune and inflammatory conditions in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The invention further provides a process for the preparation of a combination product as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable salt thereof with the other therapeutic agent that is useful in the treatment of autoimmune or inflammatory conditions, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.

By “bringing into association”, we mean that the two components are rendered suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components “into association with” each other, we include that the two components of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Compounds of the invention may be administered at varying doses. Oral, pulmonary and topical dosages (and subcutaneous dosages, although these dosages may be relatively lower) may range from between about 0.01 mg/kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day. For e.g. oral administration, the compositions typically contain between about 0.01 mg to about 2000 mg, for example between about 0.1 mg to about 500 mg, or between 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise. In particular, compounds of the invention may

have the advantage that they are more efficacious and/or exhibit advantageous properties *in vivo*.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

Examples

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed.

aq	aqueous
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
MeOH	methanol
MeCN	acetonitrile
Pd-C	palladium on carbon
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
min.	minutes
h.	hours
Hunigs base	*N,N*-diisopropylethylamine
DCM	dichloromethane
n-BuOH	butan-1-ol
iPrOH	propan-2-ol
NEt_3	triethylamine
Boc	*tert*-butoxycarbonyl

HATU	(1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo-[4,5-b]pyridinium 3-oxid hexafluorophosphate
NMP	*N*-methylpyrrolidine
LCMS	liquid-chromatography electrospray mass spectroscopy
NMR	nuclear magnetic resonance
NCS	N-chlorosuccinimide
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0)
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
$B(OMe)_3$	trimethylborate
n-BuLi	n-butyl lithium
MeI	iodomethane
NaOMe	sodium methoxide
$CHCl_3$	chloroform
$MgSO_4$	anhydrous magnesium sulphate
K_2CO_3	anhydrous potassium carbonate
NH_4OH	ammonium hydroxide
Ac_2O	acetic anhydride
$POCl_3$	phosphorus oxychloride
TBTU	O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate
CuCl	copper(I) chloride
$NaHCO_3$	sodium bicarbonate
KOH	potassium hydroxide
$PdCl_2$dppf·DCM	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
TMPMgCl·LiCl	2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex
Oxone	Potassium peroxymonosulfate

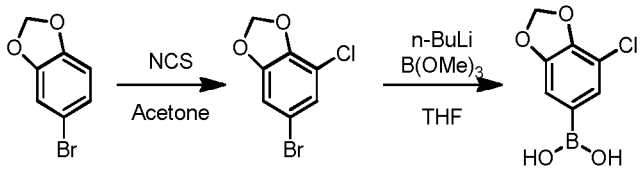
Starting materials and chemical reagents specified in the syntheses described below are commercially available, e.g. from Sigma-Aldrich, Fine Chemicals Combi-Blocks and other vendors.

In the event that there is a discrepancy between nomenclature and any compounds depicted graphically, then it is the latter that presides (unless contradicted by any experimental details that may be given or unless it is clear from the context). Final compounds were named using Marvin software versions 6.1. and 6.2. or ChemBioDraw Ultra 13.

Purification of compounds may be carried out using silica-gel column chromatography or preparative reverse phase HPLC (ACE column, acidic gradients with MeCN-H_2O containing 0.1 % TFA or XBridge column, basic gradients using MeCN-H_2O containing ammonium bicarbonate) to give the products as their free bases or trifluoroacetic acid salts.

Intermediate 1

(7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid.



Step 1: 6-bromo-4-chloro-2H-1,3-benzodioxole:

To a solution of 5-bromo-2H-1,3-benzodioxole (60 µL, 0.50 mmol, 1 equiv.) in acetonitrile (1 mL) was added 1-chloropyrrolidine-2,5-dione (73 mg, 0.55 mmol, 1.1 equiv.). The reaction was stirred overnight at room temperature. After completion of the reaction, the reaction mixture was concentrated and purified by column chromatography (Heptane/EtOAc 100 % → 5:1) to afford the desired product as a colourless solid (104 mg, 89 %). LCMS $[M+H]^+$ 234; ^1H NMR (400 MHz, CD_3OD) δ 7.05 (1H, s), 6.93 (1H, s), 2.78 (2H, s).

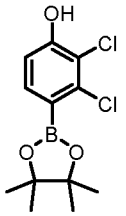
Step 2: (7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid:

To a solution of 6-bromo-4-chloro-2H-1,3-benzodioxole (104 mg, 0.44 mmol, 1 equiv.) in THF (5.8 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 265 µL, 0.66 mmol, 1.5 equiv.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (248 µL, 2.21 mmol, 5 equiv.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 3:1) to afford

the desired product as a white solid (22 mg, 25 %). LCMS $[M+H]^+$ 201; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (1H, s), 6.81 (1H, s), 5.99 (2H, s).

Intermediate 2

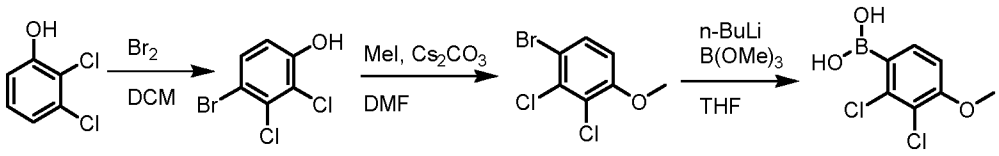
2,3-dichloro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.



To a solution of 4-bromo-2,3-dichlorophenol (250 mg, 1.03 mmol, 1 equiv.) in THF (10 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 1.25 mL, 3.10 mmol, 3 equiv.). The reaction mixture was stirred at this temperature for 30 min, before addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (316 µL, 1.55 mmol, 1.5 equiv.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 4:1) to afford the desired product as a white solid (102 mg, 34 %). LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ 7.47 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.1 Hz), 1.36 (12H, s).

Intermediate 3

(2,3-dichloro-4-methoxyphenyl)boronic acid.



Step 1: 4-Bromo-2,3-dichlorophenol.

To a solution of 2,3-dichlorophenol (1.0 g, 6.13 mmol, 1 equiv.) in DCM (4 mL) was added, at 0 °C, bromine (348 µL, 6.75 mmol, 1.1 equiv.) over 15 min. The reaction was allowed to warm up to rt over 12 hours. NMR showed unreacted starting material, bromine (0.33 equiv.) was added at 0 °C and the reaction was allowed to warm up to rt over 12 hours. The reaction was stopped by addition of $Na_2S_2O_3$, the organic layer was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column

chromatography (Pentane/EtOAc 100 % → 25:1) to afford the desired product as a white solid (685 mg, 46 %). LCMS $[M+H]^+$ 239; ^1H NMR (400 MHz, DMSO-d_6) δ 10.98 (1H, s), 7.54 (1H, d, J = 8.8 Hz), 6.91 (1H, d, J = 8.8 Hz).

Step 2: 1-Bromo-2,3-dichloro-4-methoxybenzene.

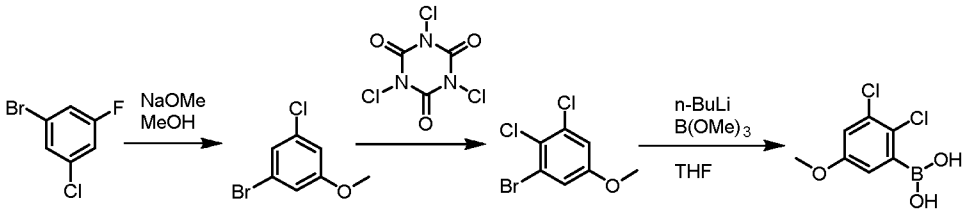
To a solution of 4-bromo-2,3-dichlorophenol (200 mg, 0.83 mmol, 1 equiv.) in DMF (3 mL) was added Cs_2CO_3 (538 mg, 1.65 mmol, 2 equiv.) followed by iodomethane (208 µL, 3.3 mmol, 4 equiv.). The reaction mixture was stirred at 70 °C for 3 h. The reaction was stopped by addition of H_2O, extracted with DCM, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 20:1) to afford the desired product as a white solid (190 mg, 89 %). LCMS $[M+H]^+$ 256; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, J = 9.0 Hz), 6.73 (1H, d, J = 8.8 Hz), 3.88 (3H, s).

Step 3: (2,3-dichloro-4-methoxyphenyl)boronic acid.

To a solution of 1-bromo-2,3-dichloro-4-methoxybenzene (100 mg, 0.39 mmol, 1 equiv.) in THF (5 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 234 µL, 0.59 mmol, 1.5 equiv.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (218 µL, 1.95 mmol, 5 equiv.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 3:1) to afford the desired product as a white solid (52 mg, 59 %). LCMS $[M+H]^+$ 221; ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (1H, s), 7.35 (1H, d, J = 8.1 Hz), 7.10 (1H, d, J = 8.1 Hz), 3.87 (3H, s).

Intermediate 4

(2,3-dichloro-5-methoxyphenyl)boronic acid.



Step 1: 1-Bromo-3-chloro-5-methoxybenzene.

1-Bromo-3-chloro-5-fluorobenzene (1 g, 4.77 mmol, 1 equiv.) was treated at 0 °C with sodium methoxide (25 % in MeOH, 1.2 mL, 5.71 mmol, 1.2 equiv.). The reaction mixture was stirred at 100 °C for 3 h. The solution was concentrated under reduced pressure, the crude product was extracted with DCM, washed with H_2O, brine, dried over $MgSO_4$ and concentrated. The product was obtained as a white solid (747 mg, 71 %). LCMS $[M+H]^+$ 220; ^1H NMR (400 MHz, CD_3Cl) δ 7.09 (1H, t, J = 1.7 Hz), 6.94 – 6.92 (1H, m), 6.83 – 6.80 (1H, m), 3.77 (3H, s).

Step 2: 1-Bromo-2,3-dichloro-5-methoxybenzene.

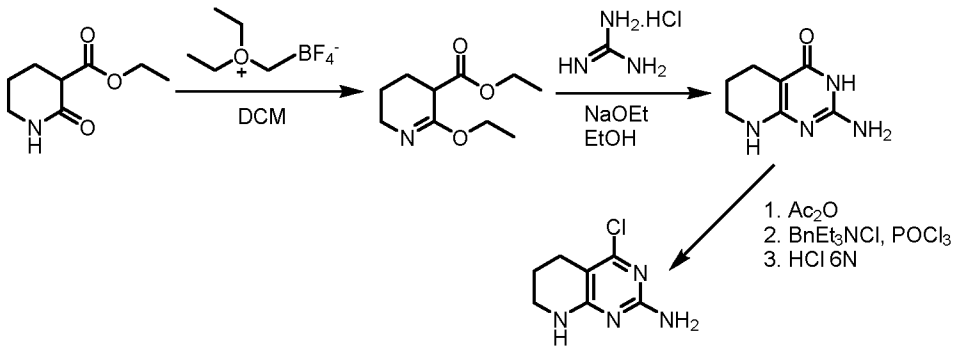
To a solution of 1-bromo-3-chloro-5-methoxybenzene (300 mg, 1.35 mmol, 1 equiv.) in DMF (5 mL) was added trichloro-1,3,5-triazinane-2,4,6-trione (115 mg, 0.49 mmol, 0.36 equiv.) and the reaction was stirred at 50 °C for 3 h. The reaction mixture was concentrated and the crude product was purified by column chromatography (Heptane/EtOAc 100 % → 20:1) to afford the desired product as a white solid (253 mg, 73 %). LCMS $[M+H]^+$ 254; ^1H NMR (400 MHz, CD_3Cl) δ 7.09 (1H, d, J = 3.0 Hz), 6.97 (1H, d, J = 3.0 Hz), 3.77 (3H, s).

Step 3: (2,3-dichloro-5-methoxyphenyl)boronic acid.

To a solution of 1-bromo-2,3-dichloro-5-methoxybenzene (87 mg, 0.34 mmol, 1 equiv.) in THF (4.5 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 205 µL, 0.51 mmol, 1.5 equiv.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (191 µL, 1.70 mmol, 5 equiv.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to afford the desired product as a white solid (75 mg, 100%). LCMS $[M+H]^+$ 221.

Intermediate 5

4-chloro-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.



Step 1: ethyl 2-ethoxy-3,4,5,6-tetrahydropyridine-3-carboxylate.

To a solution of ethyl 2-oxopiperidine-3-carboxylate (1.5 g, 8.76 mmol, 1 equiv.) in DCM (6.5 mL) under N_2 was added a solution of triethyloxonium tetrafluoroborate (2.0 g, 10.51 mmol, 1.2 equiv.) in DCM (6.5 mL). The reaction mixture was stirred at room temperature overnight. The solution was poured in water (5 mL) and allowed to stand for 30 min. The organic layer was washed with $NaHCO_3$, H_2O, dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a colourless oil (1.2 g, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (2H, q, J = 7.2 Hz), 4.00 – 3.98 (2H, m), 3.46 – 3.44 (2H, m), 3.18 – 3.16 (1H, m), 1.97 – 1.95 (2H, m), 1.68 – 1.66 (1H, m), 1.49 – 1.47 (1H, m), 1.25 (3H, t, J = 7.1 Hz), 1.20 (3H, t, J = 7.0 Hz).

Step 2: 2-amino-3H,4H,5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-4-one.

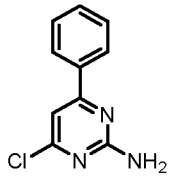
A solution of sodium ethoxide (21 % in EtOH, 197 µL, 2.51 mmol, 2.5 equiv.) was added to the mixture of ethyl 2-ethoxy-3,4,5,6-tetrahydropyridine-3-carboxylate (200 mg, 1 mmol, 1 equiv.) and guanidine hydrochloride (96 mg, 1 mmol, 1 equiv.) in EtOH (2 mL). The reaction mixture was stirred a reflux overnight. The solvent were removed under vacuum and the obtained solid was dried to afford the desired product as a light yellow solid (116 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (1H, br s), 6.18 (1H, br s), 6.10 (2H, br s), 3.10 – 3.08 (2H, m), 2.20 – 2.18 (2H, m), 1.61 – 1.59 (2H, m).

Step 3: 4-chloro-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

A mixture of 2-amino-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one and acetic anhydride was heated at reflux for 1 h until completion of the reaction as monitored by LCMS. The solvent was removed under reduced pressure and the obtained residue was treated with benzyltriethylammonium chloride (547 mg, 2.4 mmol, 2 equiv.) and $POCl_3$ (671 µL, 7.2 mmol, 6 equiv.) and heated at reflux for 1 h. After evaporation of the solvents, ice water was added to the residue and HCl (6N, 5.5 mL) was added. The reaction mixture was heated at 50 °C overnight. After evaporation of the solvents, the residue is diluted in EtOAc and washed with $NaHCO_3$, brine and dried over Na_2SO_4. The combined organic layers were then evaporated, and the crude product was purified by column chromatography (DCM/MeOH 98/2 200 mL, 95/5 100 mL). The pure product was obtained as a yellow powder (45 mg, 20 %). LCMS $[M+H]^+$ 185. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.03 (1H, br s), 3.28 – 3.26 (2H, m), 2.53 – 2.51 (2H, m), 1.81 – 1.79 (2H, m).

Intermediate 6

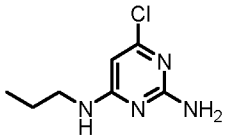
4-chloro-6-phenylpyrimidin-2-amine.



A mixture of 2-amino-4,6-dichloropyrimidine (3 g, 18.29 mmol, 1 equiv.), phenylboronic acid (2.45 g, 20.12 mmol, 1.1 equiv.), K_2CO_3 (5.06 g, 36.6 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (700 mg, 0.6 mmol, 0.03 equiv.) in 1,4-dioxane (15 mL) and water (1 mL) was heated in a sealed tube at 95°C for 12 h. The mixture was run through a plug of silica using EtOAc as eluent, concentrated and purified by column chromatography (1:4 EtOAc/pentane) to give the desired product as a white solid (2.2 g, 60 %). LCMS $[M+H]^+$ 206; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.20 (2H, m), 8.16 – 8.05 (3H, m), 7.19 (2H, s), 6.76 (1H, s).

Intermediate 7

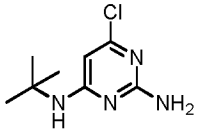
6-chloro-4-N-propylpyrimidine-2,4-diamine.



A solution of 4,6-dichloropyrimidin-2-amine (820 mg, 5.0 mmol, 1 equiv.) in EtOH (40 mL) was treated with propan-1-amine (5.0 ml). The reaction mixture was stirred at 85 ºC for 48h. The mixture was cooled, concentrated by evaporation then flash-chromatographed over silica to afford the product as a colorless solid (705 mg; 76%). LCMS $[M+H]^+$ 187.

Intermediate 8

4-N-tert-butyl-6-chloropyrimidine-2,4-diamine.

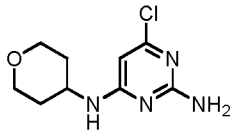


To a solution of 4,6-dichloropyrimidin-2-amine (820 mg, 5.0 mmol, 1 equiv.) in n-BuOH (20 mL) was added tert-butylamine (365 mg, 5.0 mmol, 1 equiv.) and Hünig´s base (645 mg, 5.0 mmol, 1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The mixture was cooled and some unreacted starting material

removed by filtration. The filtrate was concentrated and the residue flash-chromatographed over silica to afford the product (0.27 g; 27%). LCMS $[M+H]^+$ 201.

Intermediate 9

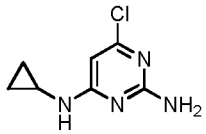
6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (492 mg, 3.0 mmol, 1 equiv.) in n-BuOH (20 mL) was added tetrahydro-2H-pyran-4-amine (303 mg, 3.0 mmol, 1 equiv.) and Hünig´s base (387 mg, 3.0 mmol, 1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The mixture was cooled and the precipitated solid was collected and washed with water to give the product (0.42 g; 37%). LCMS $[M+H]^+$ 229.

Intermediate 10

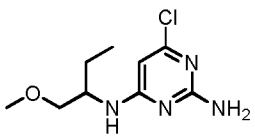
6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.0 mmol, 1 equiv.) in n-BuOH (5 mL) were added cyclopropanamine (80 µL, 1.1 mmol, 1.1 equiv.) and Hünig´s base (260 µL, 1.5 mmol, 1.5 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as an off-white solid (152 mg, 82 %). LCMS $[M+H]^+$ 185; ^1H NMR (400 MHz, DMSO-d_6) δ 7.29 (1H, s), 6.38 (2H, s), 5.85 (1H, s), 3.52 (1H, s), 0.73 – 0.64 (2H, m), 0.53 – 0.35 (2H, m).

Intermediate 11

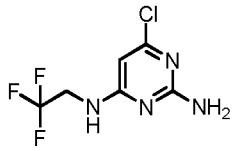
6-chloro-4-N-(1-methoxybutan-2-yl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.1 mmol, 1 equiv.) in n-BuOH (10 mL) were added 1-methoxybutan-2-amine (315 mg, 3.1 mmol, 1 equiv.) and Hünig´s base (531 µL, 3.1 mmol, 1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as an off-white solid (592 mg, 84 %). LCMS $[M+H]^+$ 231.

Intermediate 12

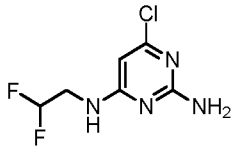
6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.00 mmol, 1 equiv.) in n-BuOH (5 mL) were added 2,2,2-trifluoroethanamine hydrochloride (149 mg, 1.1 mmol, 1.1 equiv.) and NEt_3 (202 mg, 2.0 mmol, 2 equiv.). The reaction mixture was stirred overnight at 90 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (59 mg, 26 %). LCMS $[M+H]^+$ 227.

Intermediate 13

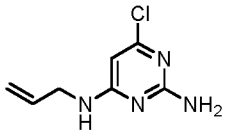
6-chloro-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.00 mmol, 1 equiv.) in n-BuOH (5 mL) were added 2,2-difluoroethanamine hydrochloride (129 mg, 1.1 mmol, 1.1 equiv.) and triethylamine (202 mg, 2.0 mmol, 2 equiv.). The reaction mixture was stirred overnight at 90 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (80 mg, 38 %). LCMS $[M+H]^+$ 209.

Intermediate 14

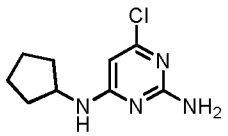
6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.04 mmol, 1 equiv.) in n-BuOH (10 mL) were added 2,2-difluoroethanamine hydrochloride (229 µL, 3.04 mmol, 1 equiv.) and Hünig´s base (584 µL, 3.35 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (471 mg, 84 %). LCMS $[M+H]^+$ 185.

Intermediate 15

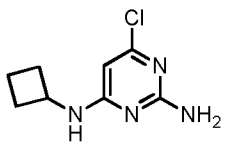
6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.04 mmol, 1 equiv.) in n-BuOH (10 mL) were added cyclopentanamine (301 µL, 3.04 mmol, 1 equiv.) and Hünig´s base (584 µL, 3.35 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a brown foam (620 mg, quantitative). LCMS $[M+H]^+$ 213.

Intermediate 16

6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine.

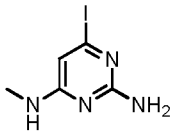


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 equiv.) in n-BuOH (5 mL) were added cyclobutanamine (130 µL, 1.52 mmol, 1 equiv.) and Hünig´s base (292 µL, 1.72 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and

concentrated to afford the desired product as a white solid (248 mg, 80 %). LCMS $[M+H]^+$ 199.

Intermediate 17

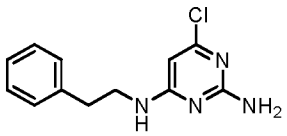
6-iodo-4-N-methylpyrimidine-2,4-diamine.



To a suspension of 6-Chloro-4-N-methylpyrimidine-2,4-diamine (1.5 g, 9.43 mmol, 1 equiv.) in acetone (6.2 mL) was added sodium iodide (7.9 g, 52.8 mmol, 5.6 equiv.) and hydrogen iodide (15 mL). The reaction mixture was stirred at 60 °C for 12 h. The solid was filtered off, dissolved in EtOAc, washed with $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired compound as an orange solid (1.7 g, 73 %). LCMS $[M+H]^+$ 251; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (1H, s), 2.80 (3H, s).

Intermediate 18

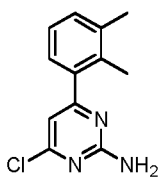
6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (66 mg, 0.40 mmol, 1 equiv.) in n-BuOH (2.5 mL) were added 2-phenylethanamine (75 µL, 0.60 mmol, 1.1 equiv.) and Hünig´s base (100 µg, 0.60 mmol, 1.1 equiv.). The reaction mixture was stirred at 95 ºC for 3 h. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (88 mg, 88 %). LCMS $[M+H]^+$ 249.

Intermediate 19

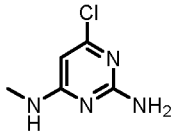
4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.



A mixture of 2-amino-4,6-dichloropyrimidine (0.82 g, 5.0 mmol, 1 equiv.), 2,3-dimethylphenylboronic acid (0.75 g, 5.0 mmol, 1 equiv.), K_2CO_3 (1.38 g, 10.0 mmol, 2 equiv.) and palladium tetrakis(triphenylphosphine)palladium (0) (0.12 g, 0.10 mmol, 0.1 equiv.) in 1,4-dioxane (20 mL) and water (5 mL) was heated in a sealed tube at 90°C for 2.5 hours. The mixture was run through a plug of silica using EtOAc as eluent, concentrated and purified by column chromatography (1:4 EtOAc/pentane) to give the desired product as a white solid (0.76 g, 65 %). LCMS $[M+H]^+$ 234; ^1H NMR (400 MHz, CD_3OD) δ 7.21 - 7.29 (1H, m), 7.20 – 7.09 (2H, m), 6.70 (1H, s), 2.34 (3H, s), 2.23 (3H, s).

Intermediate 20

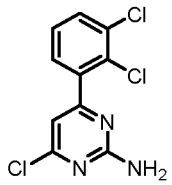
4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine.



A mixture of 4,6-dichloropyrimidin-2-amine (3.28 g, 20.0 mmol), methanamine (12.0 mL, 24.0 mmol; as a 2 M solution in methanol) and Hünig's base in n-butanol (20 mL) was heated at 95°C overnight. The mixture was concentrated and the crude was taken up in EtOAc (300 mL) and washed with water (3 x 150 mL). The organic layer was dried over MgSO4, filtered and concentrated to give the desired product as a buff solid (2.90 g, 91%). LCMS $[M+H]^+$ 159.

Intermediate 21

6-chloro-4-N-methylpyrimidine-2,4-diamine.

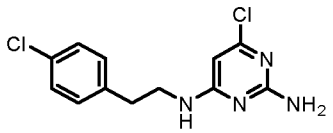


A mixture of 4,6-dichloropyrimidin-2-amine (0.50 g, 3.05 mmol), (2,3-dichlorophenyl)boronic acid (0.64 g, 3.35 mmol), sodium carbonate (0.65 g, 6.10 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (0.088 g, 0.076 mmol) in 1,4-dioxane/water (30 mL; 4:1) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was run through a plug of silica (EtOAc) and then concentrated. Purification by column chromatography (1:4→1:3 EtOAc/hexane) afforded the desired product as a white solid (0.26 g, 31%). LCMS $[M+H]^+$ 274; ^1H

NMR (400 MHz, DMSO-d_6) δ 6.89 (1H, s) 7.33 (2H, br s) 7.44 - 7.52 (2H, m) 7.71 - 7.81 (1H, m).

Intermediate 22

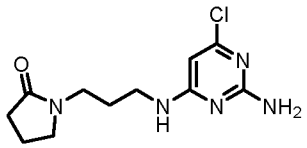
6-Chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.



A mixture of 4,6-dichloropyrimidin-2-amine (0.50 g, 3.05 mmol), 2-(4-chlorophenyl)ethan-1-amine (0.56 mL, 3.96 mmol) and Hünig's base (0.80 mL, 4.57 mmol) in n-butanol (5 mL) was heated in a sealed tube at 95°C overnight. The mixture was concentrated and the crude was taken up in EtOAc (50 mL) and washed with water (3 x 40 mL). The organic layer was dried over MgSO4, filtered and concentrated to give the desired product as a buff solid (0.61 g, 71%). LCMS $[M+H]^+$ 283.

Intermediate 23

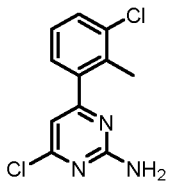
1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one.



A mixture of 4,6-dichloropyrimidin-2-amine (1.64 g, 10.0 mmol), 1-(3-aminopropyl)pyrrolidin-2-one (1.96 mL, 14.0 mmol) and Hünig's base (2.61 mL, 15.0 mmol) in n-butanol (20 mL) was heated in a sealed tube at 110°C overnight. The mixture was concentrated and the crude was taken up in EtOAc (300 mL) and washed with water (3 x 150 mL). The aqueous layers were combined and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over MgSO4, filtered and concentrated to give the desired product as a buff solid (1.63 g, 60%). LCMS $[M+H]^+$ 270.

Intermediate 24

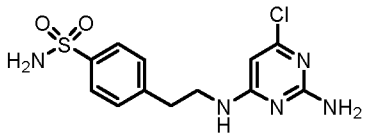
4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine.



A stirred mixture of 2-amino-4,6-dichloropyrimidine (0.50 g, 3.1 mmol), 3-chloro-2-methylphenylboronic acid (0.57 g, 3.4 mmol), Na_2CO_3 (1.0 g, 9.8 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (88 mg, 0.076 mmol), dioxane (22 mL) and water (8 mL) were heated in a sealed tube at 90°C for 2 hours. The solvents were removed in vacuo and the remaining solid was added EtOAc (20 mL) and washed with water. The organic phase was dried over $MgSO_4$ and removed in vacuo. The crude material was purified by flash chromatography (1:4 EtOAc/petroleum ether) to give the desired product as a white solid (365 mg, 47%). LCMS $[M+H]^+$ 254; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.52 - 7.56 (1 H, dd, J_1 = 6.5 Hz, J_2 = 2.5 Hz) 7.30 - 7.33 (2 H, m) 7.26 (2 H, s) 6.79 (1 H, s) 2.32 (3 H, s).

Intermediate 25

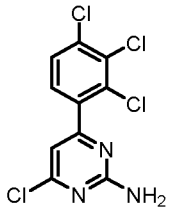
4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide.



To a suspension of 4,6-dichloropyrimidin-2-amine (800 mg, 4.9 mmol) and 4-(2-aminoethyl)benzenesulfonamide (980 mg, 4.9 mmol) in 2-propanol (10 mL), was added Hünig's base (1.0 mL, 5.7 mmol) and the resulting mixture was heated at reflux for 15 h. The mixture was then poured into $NaHCO_3$ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated and the crude mixture was purified by column chromatography to afford the title compound. LCMS $[M+H]^+$ 328; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.80 - 7.85 (m, 2 H), 7.41 (d, J=8.6 Hz, 2 H), 5.76 - 5.81 (m, 1 H), 3.54 - 3.64 (m, 2 H), 2.95 (t, J=7.1 Hz, 2 H).

Intermediate 26

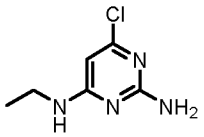
4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine.



A mixture of 4,6-dichloropyrimidin-2-amine (82 mg, 0.50 mmol), (2,3,4-trichlorophenyl)-boronic acid (113 mg, 0.50 mmol), potassium carbonate (138 mg, 1.0 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (14 mg, 0.013 mmol) in 1,4-dioxane/water (8 mL; 4:1) was heated in a sealed tube at 90°C for 2 h. The reaction mixture was run through a plug of silica (EtOAc) and then concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 308.

Intermediate 27

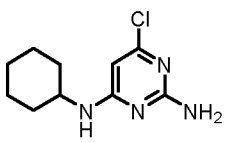
6-chloro-4-N-ethylpyrimidine-2,4-diamine



To a solution of 4,6-dichloropyrimidin-2-amine (1 g, 6.09 mmol, 1 equiv.) in n-BuOH (18 mL) were added ethaneamine (2M, 3.0 mL, 6.09 mmol, 1 equiv.) and Hünig´s base (1.17 mL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. Ethaneamine (1 eq) was added and the reaction was stirred overnight at 95 ºC until complete consumption of starting material (2 additions). The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3/^iPrOH$ (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 173; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 5.76 (1H, s), 4.79 (3H, br s), 3.26 (2H, br s), 1.20 (3H, t, J = 7.2 Hz).

Intermediate 28

6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine.

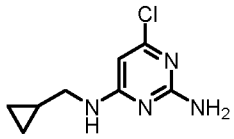


To a solution of 4,6-dichloropyrimidin-2-amine (1 g, 6.09 mmol, 1 equiv.) in n-BuOH (18 mL) were added cyclohexanamine (698 µL, 6.09 mmol, 1 equiv.) and

Hünig´s base (1.17 mL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. Cyclohexanamine (1 eq) was added and the reaction was stirred overnight at 95 ºC until complete consumption of starting material (2 additions). The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 227; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.73 (1H, s), 4.97 (2H, s), 4.79 (1H, br s), 3.45 (1H, br s), 1.97 – 1.92 (2H, m), 1.74 – 1.69 (2H, m), 1.63 – 1.58 (1H, m), 1.39 – 1.32 (2H, m), 1.22 – 1.10 (2H, m).

Intermediate 29

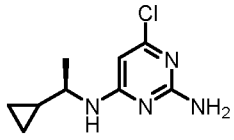
6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 equiv.) in n-BuOH (4.5 mL) were added cyclopropylmethanamine (131 µL, 6.09 mmol, 1 equiv.) and Hünig´s base (292 µL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 199; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.75 (1H, s), 4.92 (3H, br s), 3.07 (2H, s), 1.04 – 0.96 (1H, m), 0.55 – 0.49 (2H, m), 0.23 – 0.19 (2H, m).

Intermediate 30

6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine.

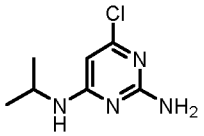


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 equiv.) in n-BuOH (4.5 mL) were added (1R)-1-cyclopropylethan-1-amine (141 µL, 6.09 mmol, 1 equiv.) and Hünig´s base (292 µL, 6.70 mmol, 1.1 equiv.). The reaction

mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a colourless oil (321 mg, 99%). LCMS $[M+H]^+$ 213; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.71 (1H, s), 4.97 (2H, s), 4.86 (1H, br s), 3.23 (1H, s), 1.19 (3H, d, J = 6.4 Hz), 0.89 – 0.81 (1H, m), 0.52 – 0.41 (2H, m), 0.31 – 0.25 (1H, m), 0.23 – 0.18 (1H, m).

Intermediate 31

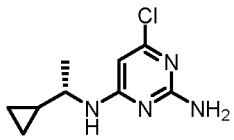
6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.05 mmol, 1 equiv.) in n-BuOH (9 mL) were added propan-2-amine (262 µL, 6.09 mmol, 1 equiv.) and Hünig´s base (584 µL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid (569 mg, 99%). LCMS $[M+H]^+$ 187; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.74 (1H, s), 4.76 (2H, s), 4.60 (1H, br s), 3.85 (1H, br s), 1.19 (3H, s), 1.18 (3H, s).

Intermediate 32

6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine.

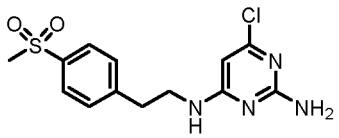


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 equiv.) in n-BuOH (4.5 mL) were added (1S)-1-cyclopropylethan-1-amine (141 µL, 6.09 mmol, 1 equiv.) and Hünig´s base (292 µL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted

twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a colourless oil (296 mg, 91%). LCMS $[M+H]^+$ 213; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.71 (1H, s), 4.99 (2H, s), 4.89 (1H, br s), 3.23 (1H, s), 1.19 (3H, d, J = 6.4 Hz), 0.88 – 0. 81 (1H, m), 0.50 – 0.40 (2H, m), 0.31 – 0.25 (1H, m), 0.23 – 0.17 (1H, m).

Intermediate 33

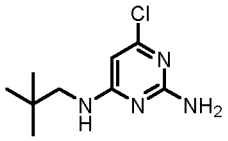
6-chloro-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.



A mixture of 4,6-dichloropyrimidin-2-amine (500 mg, 3.0 mmol), 2-(4-methylsulfonylphenyl)ethanamine (600 mg, 3.0 mmol) and Hünig's base (0.63 mL, 3.6 mmol) in 2-propanol (10 mL) was heated at reflux for 15 h. The reaction mixture was poured into $NaHCO_3$ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. The crude mixture was purified by column chromatography which afforded the title compound. LCMS [M+H]+ 327; ^{1}H NMR (400 MHz, CDCl3) δ ppm 7.90 (d, J=8.3 Hz, 2 H), 7.41 (d, J=8.3 Hz, 2 H), 5.77 (s, 1 H), 4.80 - 4.89 (m, 2 H), 4.69 - 4.79 (m, 1 H), 3.56 - 3.67 (m, 2 H), 3.07 (s, 3 H), 3.00 (t, J=6.8 Hz, 2 H).

Intermediate 34

6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine.

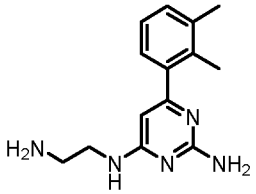


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 equiv.) in n-BuOH (9 mL) were added 2,2-dimethylpropan-1-amine (6.09 mmol, 1 equiv.) and Hünig´s base (292 µL, 6.70 mmol, 1.1 equiv.). The reaction mixture was stirred overnight at 95 ºC. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 215; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.94 (1H, s),

3.24 (2H, br s), 0.98 (9H, s).

Intermediate 35

4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.



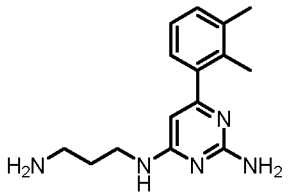
Step 1: To a suspension of 4,6-dichloropyrimidin-2-amine (500 mg, 3.05 mmol) and Hünig's base (0.80 mL) in 2-propanol (3.0 mL) was added tert-butyl N-(2-aminoethyl)carbamate (586 mg, 3.66 mmol) and the mixture was stirred at 150 °C for 15 min. The crude mixture was poured into $NaHCO_3$ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. Purification by column chromatography (0→10% MeOH in DCM) afforded tert-butyl N-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (850 mg, 2.95 mmol).

Step 2: tert-Butyl N-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (850 mg, 2.95 mmol), (2,3-dimethylphenyl)boronic acid (532 mg, 3,55 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (34 mg, 0.030 mmol), and K_2CO_3 (1020 mg, 7.39 mmol) were suspended in 1,4-dioxane (10 ml) and H_2O (2.0 ml). The vial was flushed with nitrogen and the resulting mixture was stirred at 90 °C for 16 h. The crude mixture was poured into $NaHCO_3$ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. Purification by column chromatography (0→10% MeOH in DCM) afforded tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl]carbamate (770 mg, 2.15 mmol).

Step 3: tert-Butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl]carbamate (770 mg, 2.15 mmol) was dissolved in TFA (6 mL) and the resulting mixture was stirred for 1 h at rt, after which the TFA was distilled off. Purification by column chromatography (5→30% MeOH [containing 1 v/v% NH_4OH] in DCM) afforded 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (500 mg, 1.94 mmol). LCMS $[M+H]^+$ 258.

Intermediate 36

4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.



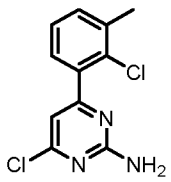
Step 1: A vial was charged with 4,6-dichloropyrimidin-2-amine (500 mg, 3.0 mmol) and tert-butyl N-(2-aminopropyl)carbamate (640 mg, 3.7 mmol). Then 2-propanol (3.0 ml) and Hünig's base (0.80 ml) were added and the resulting mixture was heated at 150 °C using microwave irradiation for 15 min. The mixture was then concentrated and purified by column chromatography (2→10% MeOH in DCM) to afford tert-butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]-carbamate (788 mg, 2.61 mmol).

Step 2: tert-Butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate (790 mg, 2.6 mmol), (2,3-dimethylphenyl)boronic acid (470 mg, 3.1 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (60 mg, 0.050 mmol), and K_2CO_3 (720 mg 5.2 mmol) were suspended in 1,4-dioxane (6.0 ml) and H_2O (1.5 ml). The resulting mixture was heated at 90 °C for 16 h and then poured into H_2O and extracted three times with DCM. The combined organic layers were dried and concentrated. Purification by column chromatography (1→10% MeOH in DCM) afforded tert-butyl N-[3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl]carbamate (800 mg, 2.1 mmol).

Step 3: tert-Butyl N-[3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl]carbamate (800 mg, 2.1 mmol) was dissolved in TFA and heated at reflux for 1 h. The TFA was evaporated and the crude residue was purified by column chromatography (2→30% MeOH [containing 1 v/v% NH_4OH] in DCM) to afford 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (540 mg, 2.0 mmol). LCMS $[M+H]^+$ 272.

Intermediate 37

4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine.

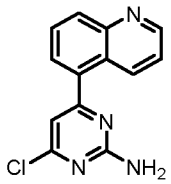


To a suspension of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq) in dioxane/H_2O (5 mL, 4:1) was added (2-chloro-3-methylphenyl)boronic acid (260

mg, 1.52 mmol, 1 eq) followed by potassium carbonate (421 mg, 3.05 mmol, 2 eq) and $Pd(PPh_3)_4$ (44 mg, 0.04 mmol, 0.025 eq). The resulting mixture was stirred at 90 ºC for 12 hrs. The solvent was removed in vacuo. The residue was taken up in DMF and purified by preparative to afford the desired product as an off-white solid (166 mg, 43%). LCMS $[M+H]^+$ 254; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.32 – 7.28 (2H, m), 7.25 – 7.21 (1H, m), 6.92 (1H, s), 5.31 (2H, br s), 2.42 (3H, s).

Intermediate 38

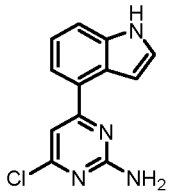
4-chloro-6-(quinolin-5-yl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (5 mL, 4:1) was added (quinolin-5-yl)boronic acid (158 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and $Pd(PPh_3)_4$ (26 mg, 0.020 mmol, 0.025 eq). The resulting mixture was stirred at 90 ºC for 12 hrs. The solvent was removed in vacuo and the residue was purified by preparative HPLC to afford the desired product as a yellow solid (63 mg, 27%). LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.21 – 9.19 (2H, m), 8.62 (1H, d, J = 8.8 Hz), 8.30 – 7.99 (1H, m), 7.92 (1H, dd, J = 7.2 and 0.8 Hz), 7.81 – 7.77 (1H, m), 6.98 (1H, s), 5.40 (2H, br s).

Intermediate 39

4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine.

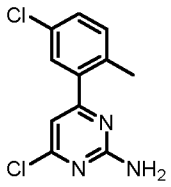


To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (5 mL, 4:1) was added (1H-indol-4-yl)boronic acid (147 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and $Pd(PPh_3)_4$ (26 mg, 0.02 mmol, 0.025 eq). The resulting mixture was stirred at 90 ºC for 12 hrs. The solvent was removed in vacuo and the residue was purified by

preparative HPLC to afford the desired product as a yellow solid (111 mg, 50%). LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.45 (1H, br s), 7.57 (1H, d, J = 7.2 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.35 (1H, t, J = 4.0 Hz), 7.27 (1H, d, J = 7.6 Hz), 7.18 (1H, s), 7.00 – 6.99 (1H, m), 5.90 (2H, br s).

Intermediate 40

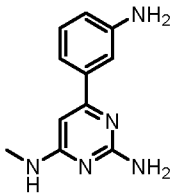
4-chloro-6-(5-chloro-2-methylphenyl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (5 mL, 4:1) was added (5-chloro-2-methylphenyl)boronic acid (155 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and $Pd(PPh_3)_4$ (26 mg, 0.02 mmol, 0.025 eq). The resulting mixture was stirred at 90 ºC for 12 hrs. The solvent was removed in vacuo and the residue was purified by preparative HPLC to afford the desired product as an off-white solid (98 mg, 42%). LCMS $[M+H]^+$ 254; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 8.4 and 2.4 Hz), 7.18 (1H, d, J = 8.4 Hz), 6.72 (1H, s), 5.30 (2H, br s), 2.34 (3H, s).

Intermediate 41

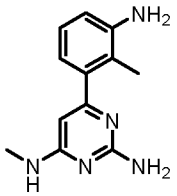
6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine.



Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.00 mmol), (3-aminophenyl)boronic acid (1.3 equiv.), sodium carbonate (3.2 equiv.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h and then concentrated. The crude material was taken up in ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, concentrated and purified by flash chromatography (0→15 % MeOH in DCM) to give the title compound. LCMS $[M+H]^+$ 216.

Intermediate 42

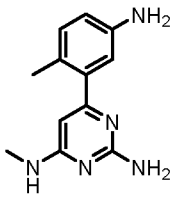
6-(3-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.



Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (3.00 mmol), (3-amino-2-methylphenyl)boronic acid (1.3 equiv.), sodium carbonate (3.2 equiv.), 1,4-dioxane (4 mL) and water (1 mL). The tube was sealed and the reaction was heated at 90°C for 5 h. The mixture was concentrated and purified by column chromatography (13% MeOH in DCM) to give the title compound. LCMS $[M+H]^+$ 230; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.88 (1 H, t, J=7.71 Hz), 6.71 - 6.81 (1 H, m), 6.61 (1 H, dd, J=7.96, 1.14 Hz), 6.44 (1 H, dd, J=7.58, 1.01 Hz), 5.90 (2 H, br. s.), 5.64 (1 H, s), 4.83 (2 H, s), 2.75 (3 H, d, J=4.55 Hz), 1.98 (3 H, s).

Intermediate 43

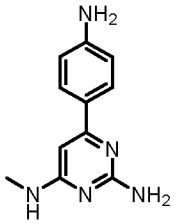
6-(5-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.



Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (3.0 mmol), (5-amino-2-methylphenyl)boronic acid (1.3 equiv.), sodium carbonate (3.2 equiv.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h. The mixture was concentrated and purified by column chromatography (13 % MeOH in DCM) to give the title compound. LCMS $[M+H]^+$ 230.

Intermediate 44

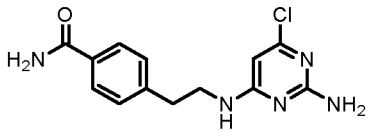
6-(4-aminophenyl)-4-N-methylpyrimidine-2,4-diamine.



Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.0 mmol), 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.3 equiv.), sodium carbonate (3.2 equiv.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h and then concentrated. The crude material was taken up in ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, concentrated and purified by flash chromatography (0→15 % MeOH/DCM) to give the title compound. LCMS $[M+H]^+$ 216; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.64 (2 H, d, J=8.53 Hz), 6.50 - 6.62 (3 H, m), 6.03 (1 H, s), 5.74 (2 H, s), 5.37 (2 H, s), 2.76 (3 H, d, J=4.77 Hz).

Intermediate 45

4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzamide



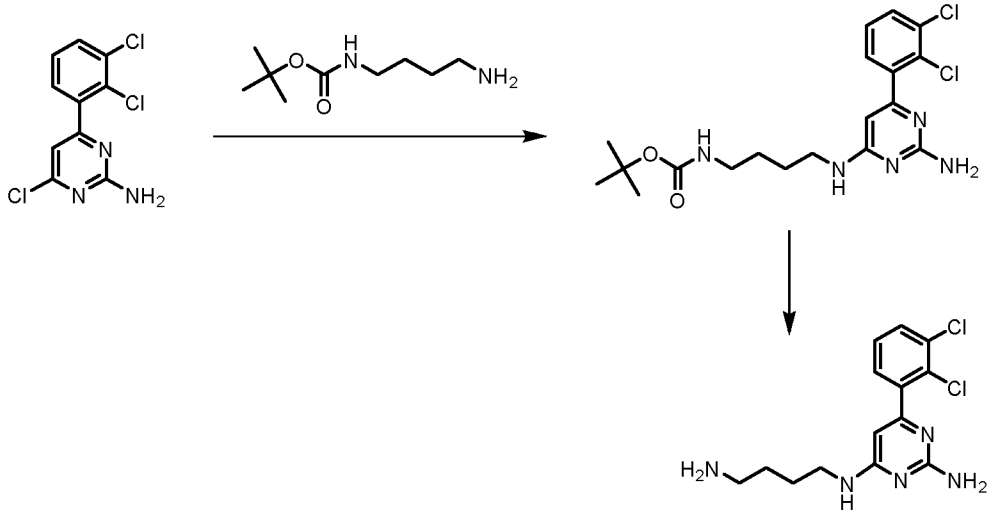
Step 1. A mixture of 2-(4-carboxyphenyl)ethylammonium chloride (1.0 equiv.), 4,6-dichloropyrimidin-2-amine (1.0 equiv.), diisopropylethylamine (3.2 equiv.), and 2-propanol was heated to 110 °C in a sealed vial for 16 h.

The mixture was concentrated and purified by silica gel chromatography which afforded 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzoic acid. LCMS $[M+H]^+$ 293.

Step 2. A mixture of 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzoic acid (1.0 equiv.), HATU (1.1 equiv.), and DMF was stirred at 20 °C for 5 min, thereafter ammonium hydroxide (3 equiv.) was added. The mixture was stirred at 20 °C for 16 h and then the mixture was diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried and purified by silica gel chromatography. $[M+H]^+$ 292.

Intermediate 46

4-N-(4-aminobutyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine



Step 1: A mixture of intermediate 21 (1 equiv.), tert-butyl N-(4-aminobutyl)carbamate (1.9 equiv.), and diisopropylethylamine (2.1 equiv.) in dioxane was stirred at 150 °C in a microwave reactor for 30 min. The crude reaction mixture was then purified by preparative LC.

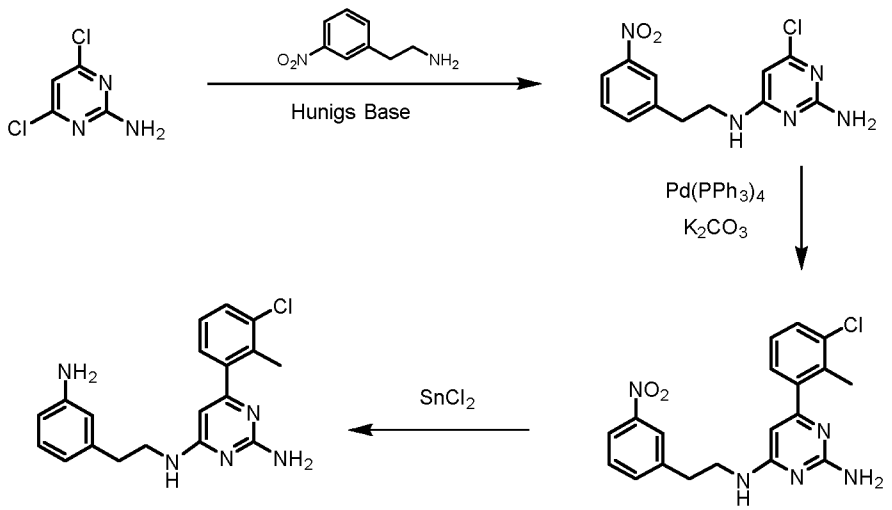
LCMS $[M+H]^+$ 426.

Step 2: tert-butyl N-[4-[[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]butyl]carbamate was stirred in TFA at 20 °C for 1 h. The TFA was then removed and the crude residue was purified by silica gel chromatography.

LCMS $[M+H]^+$ 326.

Intermediate 47

4-N-[2-(3-aminophenyl)ethyl]-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine



Step 1: A mixture of 2-amino-4,6-dichloropyrimidine (1.0 equiv.), 2-(3-

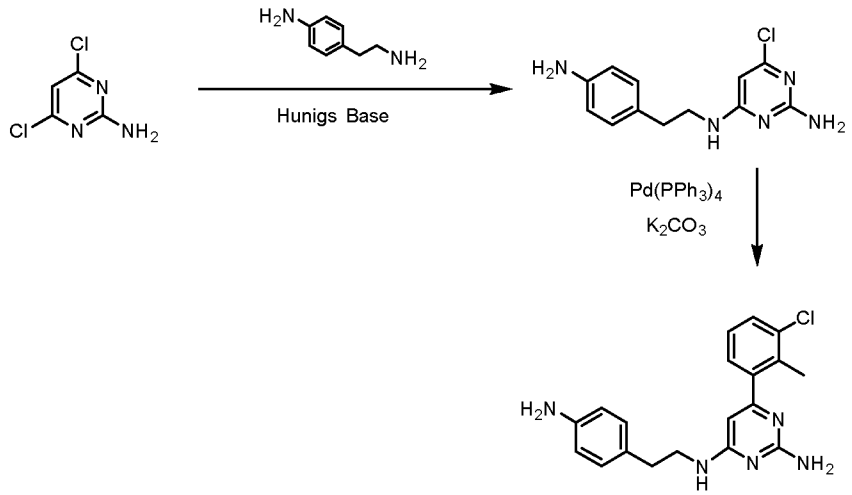
nitrophenyl)ethylammonium chloride (1.3 equiv.), and diisopropylethylamine (2.5 equiv.) in 2-propanol was stirred at 100 °C in a sealed vial for 16 h. The reaction mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM. The crude material was then purified by silica gel chromatography.

Step 2: A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-(3-nitrophenyl)ethyl]pyrimidine-2,4-diamine (1.0 equiv.), (3-chloro-2-methyl-phenyl)boronic acid (1.2 equiv.), K_2CO_3 (3.0 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in 1,4-dioxane and water was stirred at 90 °C for 16 h. Thereafter water was added and the mixture was extracted with DCM ×3. The combined organic phases were concentrated and purified by silica gel chromatography. LCMS [M+H]+ 384.

Step 3: A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-(3-nitrophenyl)ethyl]pyrimidine-2,4-diamine (1.0 equiv.) and $SnCl_2 \cdot H_2O$ (5.0 equiv.) was stirred in ethanol at reflux for 16 h. Then KOH (1 M) was added and the mixture was extracted with DCM ×5. The organics were dried, concentrated and purified by silica gel chromatography. LCMS $[M+H]^+$ 354. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.37 (d, *J*=1.6 Hz, 1 H), 7.19 (d, *J*=1.6 Hz, 1 H), 7.14 - 7.18 (m, 1 H), 7.09 - 7.14 (m, 1 H), 6.61 - 6.64 (m, 1 H), 6.54 - 6.60 (m, 2 H), 5.77 (s, 1 H), 4.77 (br. s., 3 H), 3.66 (br. s., 2 H), 3.51 - 3.62 (m, 2 H), 2.83 (t, *J*=7.0 Hz, 2 H), 2.37 (s, 3 H).

Intermediate 48

4-N-[2-(4-aminophenyl)ethyl]-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine



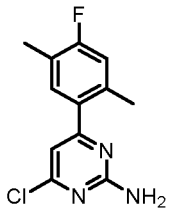
Step 1: A mixture of 2-amino-4,6-dichloropyrimidine (1.0 equiv.), 4-(2-aminoethyl)aniline (1.3 equiv.), and diisopropylethylamine (2.0 equiv.) in 2-

propanol was stirred at 90 °C in a sealed vial for 16 h. The reaction mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM. The crude material was then purified by silica gel chromatography. $[M+H]^+$ 264.

Step 2: A mixture of N4-[2-(4-aminophenyl)ethyl]-6-chloro-pyrimidine-2,4-diamine (1.0 equiv.), (3-chloro-2-methyl-phenyl)boronic acid (1.2 equiv.), K_2CO_3 (3.0 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in 1,4-dioxane and water was stirred at 90 °C for 16 h. Thereafter water was added and the mixture was extracted with DCM ×3. The combined organic phases were concentrated and purified by silica gel chromatography. LCMS $[M+H]^+$ 354.

Intermediate 49

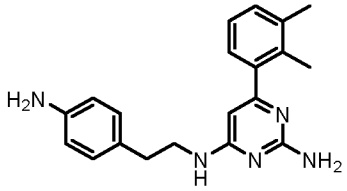
4-chloro-6-(4-fluoro-2,5-dimethylphenyl)pyrimidin-2-amine



A mixture of 2-amino-4,6-dichloropyrimidine (0.72 g, 4.4 mmol, 1 equiv.), 4-fluoro-2,5-dimethylphenylboronic acid (0.78 g, 4.6 mmol, 1 equiv.), K_2CO_3 (1.2 g, 8.8 mmol, 2 equiv.) and tetrakis(triphenylphosphine)palladium (0.17 g, 0.15 mmol, 0.033 equiv.) in 1,4-dioxane (10 mL) and water (2 mL) was heated in a sealed tube at 60°C for 23 hours. The mixture was diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were concentrated and purified by column chromatography. LCMS $[M+H]^+$ 252. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.23 (d, J=7.83 Hz, 1 H), 6.92 (d, J=10.61 Hz, 1 H), 6.73 (s, 1 H), 5.37 (br. s., 2 H), 2.37 (s, 3 H), 2.27 (d, J=0.76 Hz, 3 H).

Intermediate 50

4-N-[2-(4-aminophenyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

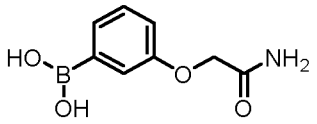


This compound was produced according to general procedure 9 from intermediate 19 and 4-(2-aminoethyl)aniline. LCMS $[M+H]^+$ 334. 1H NMR (400

MHz, CHLOROFORM-*d*) δ ppm 7.19 (br. s., 1 H), 7.13 (s, 1 H), 7.08 (s, 1 H), 7.00 (d, *J*=8.34 Hz, 2 H), 6.68 (d, *J*=8.34 Hz, 2 H), .80 (s, 1 H), 3.48 - 3.60 (m, 2 H), 2.77 (t, *J*=7.45 Hz, 2 H), 2.32 (s, 3 H), 2.20 (s, 3 H).

Intermediate 51

[3-(carbamoylmethoxy)phenyl]boronic acid

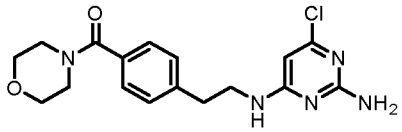


Step 1: 3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (300 mg, 1,4 mmol), 2-bromoacetamide (210 mg, 1,5 mmol), K_2CO_3 (570 mg, 4,1 mmol) and MeCN (15 mL) were heated in a sealed tube at 65°C overnight. The reaction was cooled and filtered. The solvent was removed in vacuo to afford 2-[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetamide LCMS $[M+H]^+$ 278

Step 2: 2-[3-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetamide (370 mg, 1,4 mmol), NaIO4 (870 mg, 4,1 mmol), THF (12 ml) and water (3 ml) was stirred at r.t. for 30 min. 1M HCl (1 mL) was added and the reaction was stirred at r.t. for 3 hours. Water (~15 mL) was added and the organic solvent was removed in vacuo. [3-(carbamoylmethoxy)phenyl]boronic acid was collected by filtration. LCMS $[M+H]^+$ 196.

Intermediate 52

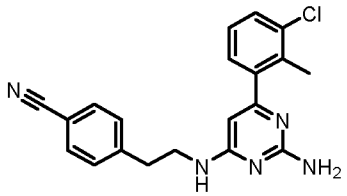
[4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]phenyl]-morpholino-methanone



A mixture of 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzoic acid (from step 1 of the synthesis of intermediate 45 and TBTU in DMF was stirred at 20 °C for 10 min, then morpholine was added and the resulting mixture was stirred at 20 °C for 20 h. The mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM ×3. The combined organics were dried, concentrated, and purified by silica gel chromatography. $[M+H]^+$ 362.

Intermediate 53

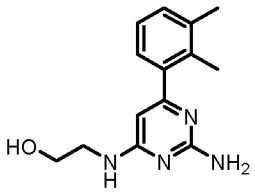
4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzonitrile



A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (150 mg, 0.59 mmol), 4-(2-aminoethyl)benzonitrile hydrochloride (110 mg, 0.59 mmol), K_2CO_3 (240 mg, 1.8 mmol) and MeCN (5 mL) was heated for 1 hour at 170 °C in a sealed vial. Thereafter the mixture was diluted with MeOH and purified by preparative LC to afford 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzonitrile. LCMS $[M+H]^+$ 364.

Intermediate 54

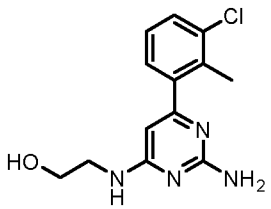
2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethan-1-ol



A mixture of Intermediate 19 (1.0 equiv.) and 2-aminoethanol (2.2 equiv.) in ethanol was heated in a sealed tube at 130 °C for 4 h. After cooling a precipitate formed which was filtered and washed with cold ethanol and dried to furnish the title compound. LCMS $[M+H]^+$ 259. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.12 - 7.17 (m, 1 H), 7.08 (t, J=7.5 Hz, 1 H), 7.00 - 7.05 (m, 1 H), 6.88 (br. s., 1 H), 5.93 (s, 2 H), 5.73 (s, 1 H), 4.74 (t, J=5.3 Hz, 1 H), 3.51 (q, J=5.8 Hz, 2 H), 3.28 - 3.33 (m, 2 H), 2.26 (s, 3 H), 2.15 (s, 3 H).

Intermediate 55

2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol

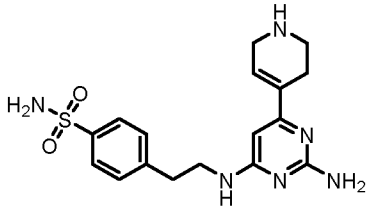


A mixture of Intermediate 24 (1.0 equiv.) and 2-aminoethanol (2.2 equiv.) in isopropanol was heated in a sealed tube at 130 °C for 1 h. After cooling a

precipitate formed which was filtered and washed with cold isopropanol and dried to furnish the title compound. LCMS $[M+H]^+$ 279.

Intermediate 56

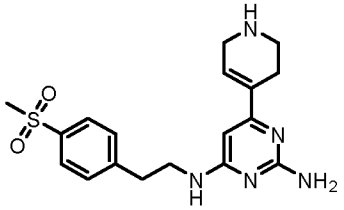
4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]-benzenesulfonamide



To tert-butyl 4-[2-amino-6-[2-(4-sulfamoylphenyl)ethylamino]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate was added 5 M HCl in dioxane and methanol and the mixture was stirred at rt for 40 min. The solvent was removed to obtain the title compound. LCMS $[M+H]^+$ 375.

Intermediate 57

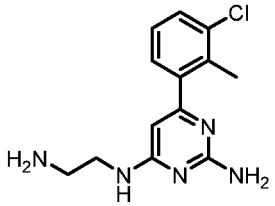
4-N-[2-(4-methanesulfonylphenyl)ethyl]-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2,4-diamine



To tert-butyl 4-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate was added HCl (5 M) in 1,4-dioxane), then the mixture was stirred at 20 °C for 20 min. The solvent was removed to obtain the title compound. LCMS $[M+H]^+$ 374.

Intermediate 58

N4-(2-aminoethyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine



Step 1. A mixture of 4,6-dichloropyrimidin-2-amine (1 equiv.), tert-butyl N-(2-

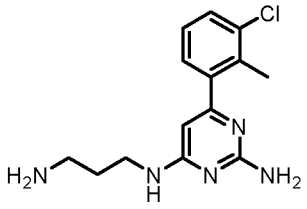
aminoethyl)carbamate (1.2 equiv.), and diisopropylethylamine (3 equiv.) in 2-propanol was stirred at 90 °C for 16 h. The reaction mixture was then poured into water and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was used in step 2 without further purification.

Step 2. The crude material from step 1 was dissolved in dioxane, then K_2CO_2 (2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), and (3-chloro-2-methyl-phenyl)boronic acid (1.2 equiv.) were added. The flask was flushed with N2 and the mixture was stirred at reflux for 16 h. The reaction mixture was then poured into water and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography using MeOH (0 – 9%) in DCM.

Step 3. The material from step 2 was dissolved in TFA and stirred at 20 °C for 2 h. The solvent was removed and the crude residue was purified by silica gel chromatography using 5 – 30% MeOH (containing 1% v/v NH_4OH) in DCM. LCMS $[M+H]^+$ 278. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.97 (br. s., 2 H), 7.62 - 7.70 (m, 1 H), 7.38 - 7.44 (m, 1 H), 7.33 - 7.37 (m, 1 H), 7.27 (br. s., 1 H), 7.14 (br. s., 1 H), 7.01 (br. s., 1 H), 6.08 (s, 1 H), 3.61 (d, *J*=4.7 Hz, 2 H), 3.10 (br. s., 2 H), 2.31 (s, 3 H).

Intermediate 59

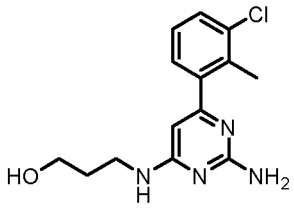
N4-(3-aminopropyl)-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine



A mixture of tert-butyl N-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propyl]carbamate (prepared in example 668) and TFA was stirred at 20 °C for 2 h, thereafter the solvent was removed by co-evaporation with 2-propanol. The crude residue was purified by silica gel chromatography. LCMS $[M+H]^+$ 292.

Intermediate 60

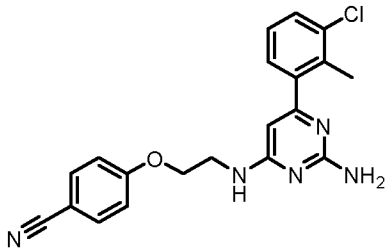
3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propan-1-ol



A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24), 3-aminopropan-1-ol (2.2 equiv.) in 2-propanol was microwave heated in a sealed tube at 130°C for 30 min. Purification by column chromatography afforded the title compound (10% MeOH in DCM). LCMS $[M+H]^+$ 293.

Intermediate 61

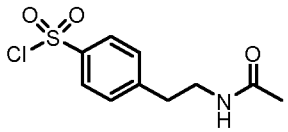
4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)benzonitrile.



A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24), 4-(2-aminoethoxy)benzonitrile (1.5 equiv.) and N,N-Diisopropylethylamine (2 equiv.) in 2-propanol (0.3 mL) was heated in a sealed tube at 100°C for 30 h. Purification by column chromatography afforded the title compound (70% EtOAc in iso-Hexane). LCMS $[M+H]^+$ 380. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.82 (m, 2 H), 7.44 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.17 - 7.28 (m, 3 H), 7.15 (d, *J*=8.8 Hz, 2 H), 6.10 (br. s., 2 H), 5.79 (s, 1 H), 4.20 (t, *J*=5.7 Hz, 2 H), 3.60 - 3.76 (m, 2 H), 2.29 (s, 3 H),

Intermediate 62

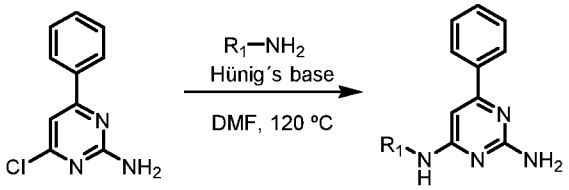
4-(2-acetamidoethyl)benzene-1-sulfonyl chloride



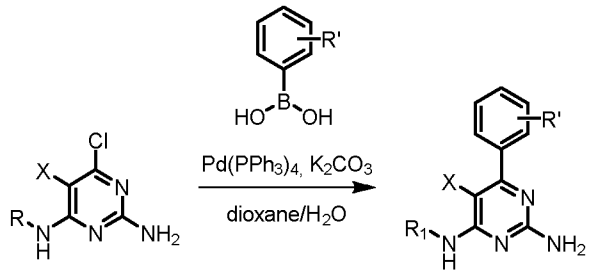
Chlorosulfuric acid (5 equiv.) was slowly added to N-(2-phenylethyl)acetamide (1 equiv.). The mixture was stirred for 2 hours at r.t. and dropped on a mixture of

water and ice. The title compound was collected by filtration and washed with water. LCMS $[M+H]^+$ 262.

General procedures

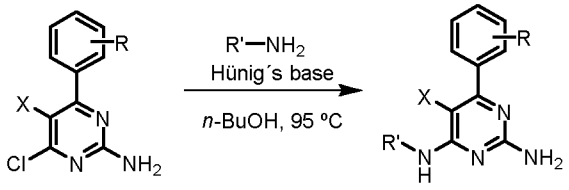


General Procedure 1: To a mixture of 4-chloro-6-phenylpyrimidin-2-amine (1 equiv.) is added Hünig´s base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in DMF (500 µL). The mixture is heated at 120 °C overnight. The crude mixture is purified by preparative HPLC to afford the desired product.



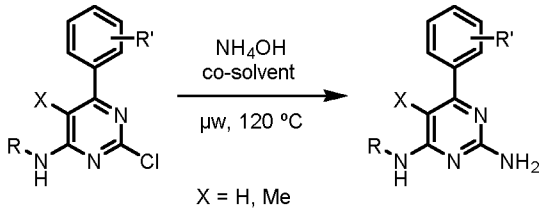
X = H or Me

General Procedure 2: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) in 1,4-dioxane/water (4:1) is added the appropriate boronic acid (or boronic ester) derivative (1.3 equiv.), K_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 95 °C overnight or in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is purified by preparative HPLC to afford the desired product.

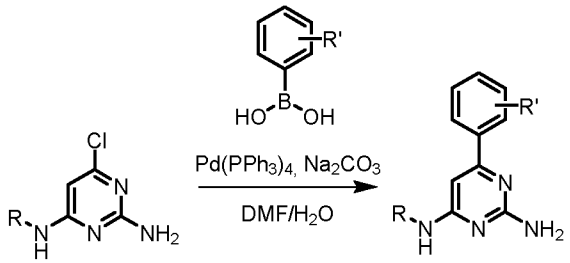


X = H, Me

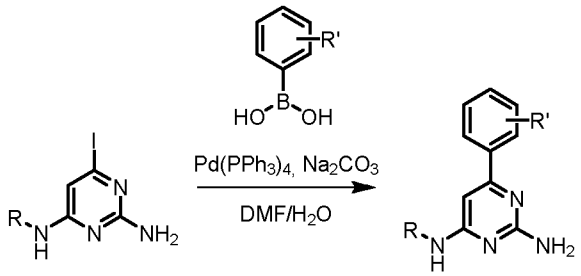
General Procedure 3: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) is added Hünig´s base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in *n*-BuOH (500 µL). The mixture is heated at 95 °C overnight. The crude mixture was purified by preparative HPLC to afford the desired product.



General Procedure 4: A solution of an appropriate chloropyrimidine derivative (1 equiv.) in ammonium hydroxide (25% aq) is heated in the microwave at 120 °C until completion of the reaction as monitored by LCMS. The solvent is then evaporated and the product is dried under vacuum. Further purification by preparative HPLC is performed when required.

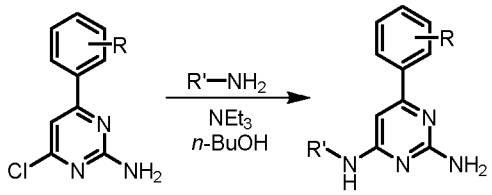


General Procedure 5: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) in DMF/water (9:1) is added the appropriate boronic acid (or boronic ester) derivative (1.1 equiv.), Na_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 120 °C overnight or in the microwave until the reaction is complete as shown by LCMS. The crude mixture is then purified by preparative HPLC to afford the desired product.

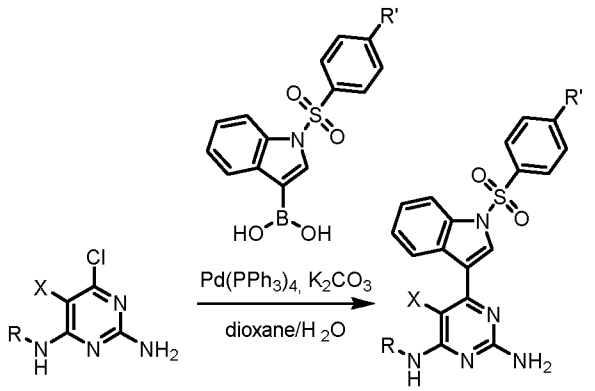


General Procedure 6: To a mixture of a suitable iodopyrimidine derivative (1 equiv.) in DMF/water (20:1) is added the appropriate boronic acid (or boronic ester) derivative (1.3 equiv.), Na_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 120 °C overnight or in a microwave reactor until the reaction

is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product.

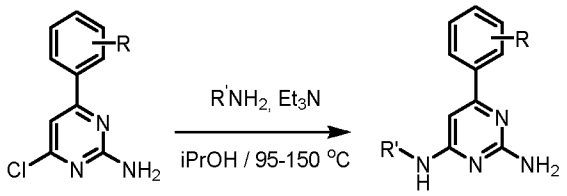


General procedure 7: A mixture of a suitable 6-aryl-4-chloropyrimidin-2-amine (1 equiv.), a suitable amine (1.5 equiv.) and triethylamine (2 equiv.) in *n*-butanol (1.5 mL) is heated in a sealed tube at 95°C overnight. Concentrated and purified by preparative HPLC to give the desired product.



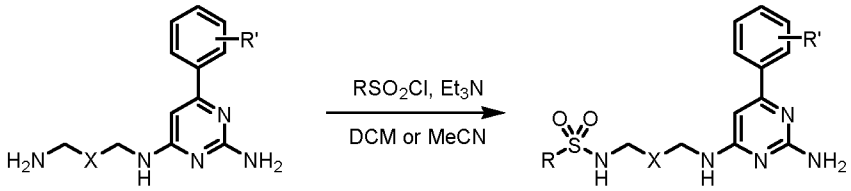
X = H or Me

General Procedure 8: To a mixture of a suitable 4-chloropyrimidin-2-amine (1 equiv.) in 1,4-dioxane/water (4:1) is added the desired boronic acid (or boronic ester) (1.3 equiv.), K_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 95 ºC overnight or in a microwave until the reaction is complete as shown by LCMS. The crude mixture is purified by HPLC to afford the desired product.



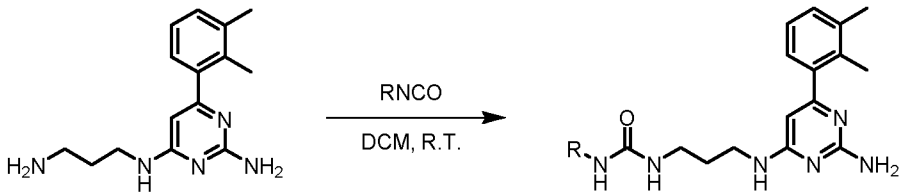
General procedure 9: A mixture of a suitable amine (1 equiv.), and a suitable chloropyrimidine derivative (1.2 equiv.) and triethylamine (1.5 equiv.) in 2-propanol (1.0 mL) is heated in a sealed tube at 95 °C overnight or at 150 °C for

15 min in a microwave reactor. The reaction mixture is then concentrated and purified by preparative HPLC or by silica gel chromatography.

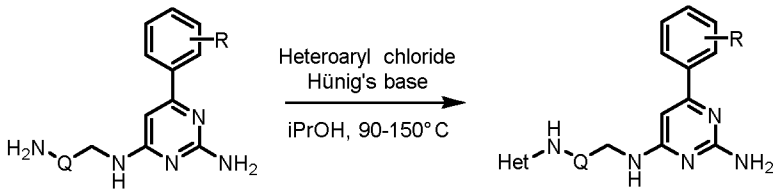


X = CH_2, CH_2CH_2, $CH(CH_3)_2$ or a bond

General procedure 10: A mixture of an 4-N-(aminoalkyl)-6-(aryl)pyrimidine-2,4-diamine (1.0 equiv.), a suitable sulfonyl chloride (1.2 equiv.), and triethylamine (1.5 equiv.) in DCM or MeCN (1.0 mL) is stirred in a sealed tube at rt or 50 °C. After completion the crude mixture is concentrated and purified by preparative HPLC or by silica gel chromatography.



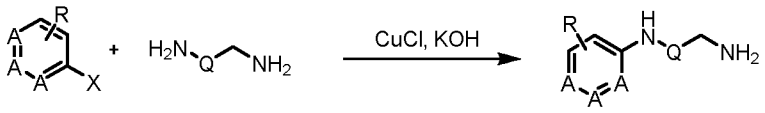
General procedure 11: A mixture of 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 equiv.) and the corresponding isocyanate (1.05 equiv.) is dissolved in DCM. The resulting reaction mixture is stirred at room temperature until completion according to LCMS. The mixture is then concentrated and purified by preparative HPLC or by silica gel chromatography.



Q = CH_2, CH_2CH_2, $C(CH_3)_2CH_2$

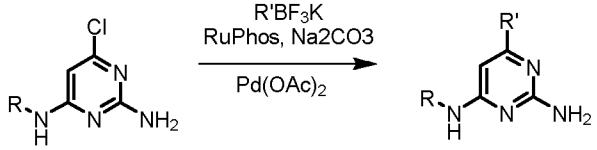
General procedure 12: A mixture of the corresponding 4-N-(aminoalkyl)-6-(aryl)pyrimidine-2,4-diamine (1.0 equiv.) and the corresponding heteroaryl chloride (1.5 equiv.), and Hünig´s base (1.5 equiv.) in 2-propanol was stirred in a sealed tube at 90 – 150 °C until the reaction was complete. The crude mixture

was then concentrated and purified by preparative LC or by silica gel chromatography.

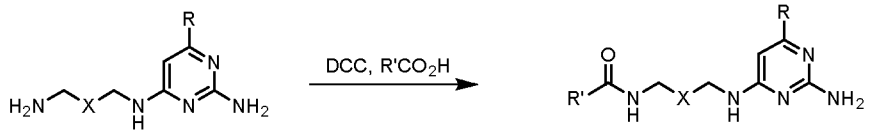


A = CH or N
X = I or Br
Q = CH_2 or CH_2CH_2

General procedure 13: A mixture of the corresponding aryl halide or heteroaryl halide (1.0 equiv.), CuCl (0.10 equiv.), KOH (2.0 equiv.), and ethylenediamine or propane-1,3-diamine (4.5 equiv.) was stirred at 20 □C (for aryl iodides) or 90 □C (for aryl bromides) for 12 – 24 h in a sealed vial. The mixture was allowed to cool and was then extracted with hot EtOAc (×5). The combined organics were concentrated and the excess of diamine was removed by co-evaporation with toluene. The crude material was used without further purification.

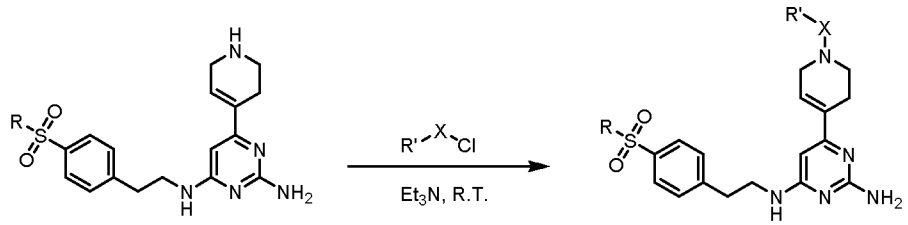


General procedure 14: A mixture of the corresponding 6-chloro-4-N-(alkyl)-pyrimidine-2,4-diamine compound (1.0 equiv.), the appropriate potassium (aryl)trifluoroborate (2.0 equiv.), $Pd(OAc)_2$ (0.10 equiv.), RuPhos (0.20 equiv), and Na_2CO_3 (3.0 equiv.) was stirred in ethanol at reflux for 16 h. The crude mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM ×3. The crude material was purified by preparative LC or by silica gel chromatography.

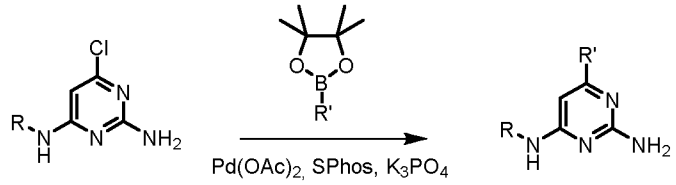


X = CH_2, CH_2CH_2, $C(CH_3)_2$ or a bond

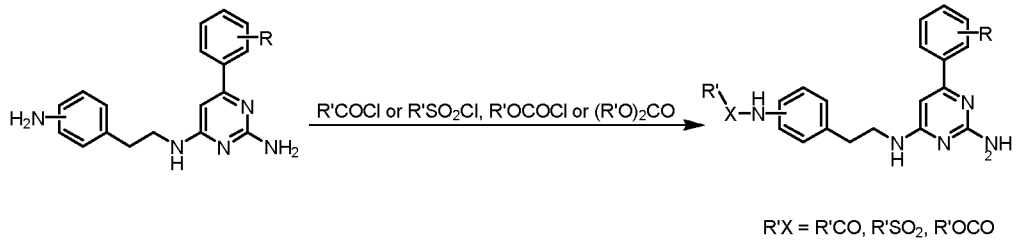
General procedure 15: A mixture of the corresponding 4-N-(aminoalkyl)-6-(aryl)pyrimidine-2,4-diamine (1 equiv.), a suitable carboxylic acid (2.0 equiv.), and dicyclohexylcarbodiimide (1.0 equiv) were stirred in acetonitrile at 20 °C for 12-24 h. The crude mixture was then purified by preparative LC or by silica gel chromatography.



General procedure 16: A mixture of an N4-[2-(4-methylsulfonylphenyl)ethyl]-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2,4-diamine hydrochloride or 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride, a suitable sulfonyl chloride or acid chloride (1.2 equiv.), and triethylamine (3.0 equiv.) in DCM was stirred in a sealed tube at rt. After completion the crude mixture was purified by preparative HPLC.

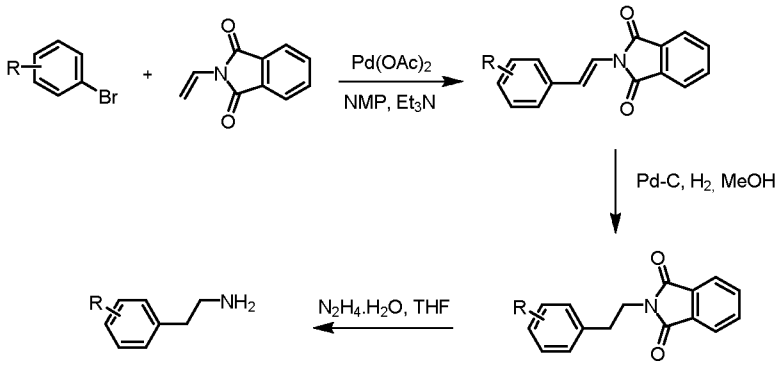


General procedure 17: A mixture of the corresponding 6-chloro-4-N-(alkyl)-pyrimidine-2,4-diamine compound (1.0 equiv.), the appropriate arylboronic ester (1.5 equiv.), $Pd(OAc)_2$ (0.10 equiv.), SPhos (0.20 equiv), and K_3PO_3 (3.0 equiv.) was stirred in a suitable solvent (ethanol or a 5:2 mixture of 1-butanol and water) at 80 – 100 °C until LCMS indicated full conversion. The crude mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM ×3. The crude material was purified by preparative LC or by silica gel chromatography.



General procedure 18: A mixture of the corresponding 4-N-(aminophenethyl) 6-(aryl)pyrimidine-2,4-diamine (1.0 equiv.), a suitable electrophile (acid chloride, sulfonyl chloride, chloroformate, or carbonate) (1.3 equiv.), and triethylamine or diisopropylethylamine (5 equiv.) in DCM or acetonitrile was stirred at 20 – 50 °C

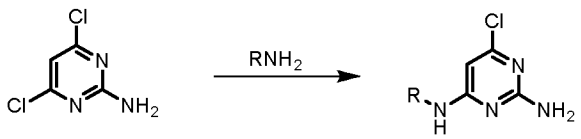
for 12 – 24 h. After completion the mixture was concentrated and purified by preparative LC or by silica gel chromatography.



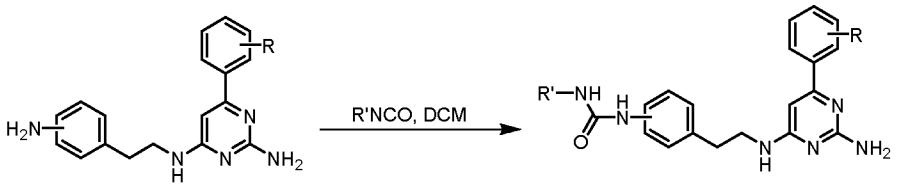
General procedure 19: Step 1: A mixture of the corresponding aryl halide (1.0 equiv.), N-vinylphthalimide (1.1 equiv.), $Pd(OAc)_2$ (0.0005 equiv.), and Et_3N (1.2 equiv.) were dissolved in NMP and stirred at 135 °C for 16 h. The reaction mixture was cooled to room temperature and then water was added which precipitated a solid. The solid was filtered off and washed with water.

Step 2: In a flask, the solid from step 1 was dissolved in MeOH and then Pd/C (0.10 eqiv.) was added. The atmosphere in the flask was changed to H_2 and the resulting mixture was stirred at 60 °C for 16 – 24 h. The solution was then passed through a syringe filter and concentrated.

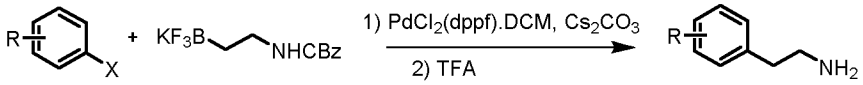
Step 3: The crude material from step 2 was dissolved in THF, and then hydrazine hydrate (1.25 equiv.) was added. The resulting mixture was stirred at reflux for 16 – 24 h. The reaction mixture was concentrated and purified by preparative LC.



General procedure 20: A mixture of 2-amino-4,6-dichloropyrimidine (1.0 equiv.), the corresponding amine (0.8 – 2.0 equiv.), and a base (K_2CO_3, Cs_2CO_3, triethylamine or diisopropylethylamine) (1.2 – 3.0 equiv.) in a suitable solvent (acetonitrile, methanol, 2-propanol, 1-butanol, DMF or DMSO) was stirred at 60 – 150 °C in a sealed vial until LCMS indicated that the reaction was complete. The reaction mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM or EtOAc. The crude material was then purified by preparative LC or by silica gel chromatography.



General procedure 21: A mixture of the corresponding amine, a suitable isocyanate, and DCM was stirred at 20 – 60 °C for 1 – 48 hours. Thereafter the mixture was concentrated and purified by preparative LC or by silica gel chromatography.



General procedure 22: Step 1. A mixture of the corresponding aryl halide (1.0 equiv.), potassium 2-(benzyloxycarbonylamino)ethyl-trifluoro-boranuide (1.0 equiv.), $PdCl_2$(dppf).DCM (0.05 equiv.), and Cs_2CO_3 (3.0 equiv.) in toluene and water was stirred at 90 °C under N_2 for 16 h. The reaction mixture was then poured into water and extracted with DCM. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography.

Step 2. The material from step 1 was stirred in refluxing TFA until the reaction was complete. The solvent was removed by co-evaporation with 2-propanol. The crude material was used without further purification.

EXAMPLES

Example 1

4-N-cyclohexyl-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclohexanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 – 8.61 (1H, m), 7.78 – 7.67 (2H, m), 7.66 – 7.55 (3H, m), 6.33 (1H, s), 4.05 – 3.85 (1H, m), 2.00 – 1.83 (2H, m), 1.80 – 1.70 (2H, m), 1.41 – 1.10 (6H, m).

Example 2

4-N-ethyl-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from ethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (1H, s), 7.74 – 7.71 (2H, m), 7.67 – 7.57 (3H, m), 6.33 (1H, s), 3.53 – 3.41 (2H, m), 1.18 (3H, t, J = 7.1 Hz).

Example 3

4-N-(3-ethoxypropyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from 3-ethoxypropan-1-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (1H, s), 7.74 – 7.71 (2H, m), 7.63 – 7.59 (3H, m), 6.37 (1H, s), 3.45 – 3.41 (6H, m), 1.80 (2H, q, J = 6.5 Hz), 1.11 (3H, t, J = 6.5 Hz).

Example 4

6-phenyl-4-N-propylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from phenylboronic acid and 6-chloro-4-N-propylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229.

Example 5

6-(4-methanesulfonylphenyl)-4-N-propylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methanesulfonylphenyl)boronic acid and 6-chloro-4-N-propylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 307; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 – 8.11 (2H, m), 8.05 – 7.92 (2H, m), 6.42 (1H, s), 3.50 – 3.40 (2H, m), 3.31 (3H, s), 1.68 – 1.51 (2H, m), 0.94 (3H, t, J = 7.1 Hz).

Example 6

4-N-(cyclopropylmethyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclopropylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 241; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (1H, s), 7.83 – 7.50 (5H, m), 6.39 (1H, s), 3.33 – 3.20 (2H, m), 1.15 – 0.95 (1H, m), 0.51 (1H, d, J = 5.8 Hz), 0.27 (1H, d, J = 5.8 Hz).

Example 7

4-N-(oxan-4-yl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from oxan-4-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 271.

Example 8

4-N-(furan-2-ylmethyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from furan-2-ylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 267.

Example 9

4-N-(pentan-3-yl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from pentan-3-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 257.

Example 10

6-phenyl-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 1 from propan-2-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 229.

Example 11

4-N-benzyl-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from phenylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 277; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.92 – 7.84 (2H, m), 7.48 – 7.40 (4H, m), 7.37 – 7.27 (4H, m), 7.27 – 7.20 (1H, m), 6.29 (1H, s), 6.06 (2H, s), 4.54 (2H, d, J = 5.9 Hz).

Example 12

4-N-[2-(morpholin-4-yl)ethyl]-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from 2-(morpholin-4-yl)ethan-1-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 300.

Example 13

6-(4-chlorophenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclopropanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 261.

Example 14

4-N-tert-butyl-6-(4-chlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 277; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.38 (1H, s), 7.75 – 7.66 (4H, m), 6.38 (1H, s), 1.46 (9H, s).

Example 15

6-(4-chlorophenyl)-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 305.

Example 16

4-N-cyclopropyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]-boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 295.

Example 17

4-N-tert-butyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.65 (2H, d, J = 9.4 Hz), 7.15 (2H, d, J = 9.4 Hz), 6.35 (1H, s), 3.85 (3H, s), 1.45 (9H, s).

Example 18

4-N-cyclopropyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.79 – 7.72 (2H, m), 7.17 – 7.15 (2H, m), 6.24 (1H, s), 3.85 (4H, s), 0.83 – 0.81 (2H, m), 0.62 – 0.60 (2H, m).

Example 19

6-(3-chlorophenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.78 – 7.76 (1H, m), 7.64 – 7.57 (3H, m), 6.27 (1H, s), 0.89 – 0.87 (2H, m), 0.70 – 0.63 (3H, m).

Example 20

4-N-tert-butyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 311.

Example 21

6-(3-chlorophenyl)-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 305; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.78 – 7.76 (1H, m), 7.65 – 7.63 (2H, m), 7.59 – 7.57 (1H, m), 6.30 (1H, s), 4.30 – 4.28 (1H, m), 4.02 – 3.98 (2H, m), 3.53 – 3.51 (2H, m), 2.01 – 2.00 (2H, m), 1.65 – 1.63 (2H, m).

Example 22

4-N-tert-butyl-6-(3-chlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 277; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 – 7.73 (1H, m), 7.65 – 7.62 (2H, m), 7.59 – 7.55 (2H, m), 1.52 (9H, s).

Example 23

4-N-methyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 394; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.36 (1H, s), 8.07 (1H, d, J = 8.3 Hz), 7.93 (2H, d, J = 8.3 Hz), 7.83 (1H, d, J = 7.9 Hz), 7.51 – 7.44 (1H, m), 7.43 – 7.31 (3H, m), 6.46 (1H, s), 3.04 (3H, s), 2.37 (3H, s).

Example 24

6-(2,3-dichlorophenyl)-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (2,3-dichlorophenyl)boronic acid and 6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 337.

Example 25
6-(3-chlorophenyl)-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 303.

Example 26
6-[1-(benzenesulfonyl)-1H-indol-3-yl]-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 380; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 – 8.25 (2H, m), 8.10 – 8.03 (2H, m), 8.01 – 7.95 (1H, m), 7.77 – 7.68 (1H, m), 7.66 – 7.56 (2H, m), 7.46 – 7.26 (2H, m), 6.74 (1H, br s), 6.32 (1H, s), 6.02 (2H, s), 2.81 (3H, d, J = 5.0 Hz).

Example 27
4-N-cyclopropyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.
Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 420; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.14 (1H, s), 8.07 (1H, d, J = 7.9 Hz), 8.01 (1H, d, J = 8.2 Hz), 7.86 (2H, d, J = 8.2 Hz), 7.43 – 7.23 (4H, m), 6.43 (1H, s), 2.65 (1H, s), 2.34 (3H, s), 0.88 – 0.74 (2H, m), 0.65 – 0.48 (2H, m).

Example 28
6-[1-(benzenesulfonyl)-1H-indol-3-yl]-4-N-cyclopropylpyrimidine-2,4-diamine.
Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 406; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.16 (1H, s), 8.10 – 7.98 (4H, m), 7.66 – 7.58 (1H, m), 7.56 – 7.46 (2H, m), 7.43 – 7.25 (2H, m), 6.43 (1H, s), 2.66 (1H, s), 0.84 – 0.81 (2H, m), 0.58 – 0.55 (2H, m).

Example 29

6-[1-(benzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 381; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.55 (1H, d, J = 8.2 Hz), 8.41 – 8.30 (2H, m), 8.22 – 8.11 (2H, m), 7.71 – 7.61 (1H, m), 7.57 – 7.50 (2H, m), 7.37 – 7.28 (1H, m), 6.27 (1H, s), 2.92 (3H, s).

Example 30

6-[1-(benzenesulfonyl)-1H-indol-4-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-4-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 380; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.08 (1H, d, J = 8.2 Hz), 7.97 – 7.89 (2H, m), 7.73 (1H, d, J = 3.8 Hz), 7.65 – 7.56 (1H, m), 7.53 – 7.45 (3H, m), 7.39 (1H, t, J = 8.2 Hz), 7.10 (1H, d, J = 3.8 Hz), 6.10 (1H, s), 2.89 (3H, s).

Example 31

6-[1-(benzenesulfonyl)-1H-indol-5-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-5-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 380; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.07 – 7.99 (2H, m), 7.98 – 7.89 (2H, m), 7.83 – 7.74 (1H, m), 7.71 (1H, d, J = 4.0 Hz), 7.64 – 7.55 (1H, m), 7.54 – 7.45 (2H, m), 6.80 (1H, d, J = 4.0 Hz), 6.21 (1H, s), 2.90 (3H, s).

Example 32

6-(2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-methoxyphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.50 (1H, dd, J = 7.5 and 1.7 Hz), 7.41 – 7.36 (1H, m), 7.08 (1H, d, J = 8.3 Hz), 7.01 (1H, td, J = 7.5 and 1.0 Hz), 6.17 (1H, s), 3.84 (3H, s), 2.89 (3H, s).

Example 33

6-(4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231.

Example 34

6-[3,5-bis(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3,5-bis(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 337; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.31 (2H, s), 8.17 (1H, s), 7.55 – 7.20 (3H, br s), 6.45 (1H, s), 3.02 (3H, s).

Example 35

6-(isoquinolin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (isoquinolin-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 252; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 9.17 (1H, s), 8.78 (1H, s), 8.17 (1H, d, J = 8.4 Hz), 8.12 (1H, d, J = 8.1 Hz), 7.98 – 7.94 (1H, m), 7.80 – 7.77 (1H, m), 6.54 (1H, s), 3.10 (3H, s).

Example 36

4-N-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [4-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.93 – 7.87 (4H, m), 6.38 (1H, s), 3.04 (3H, s).

Example 37

4-N-methyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.05 (1H, s), 7.99 (1H, d, J = 8.0 Hz), 7.92 (1H, d, J = 8.0 Hz), 7.79 (1H, t, J = 8.0 Hz), 6.38 (1H, s), 3.05 (3H, s).

Example 38

6-(2,3-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.79 – 7.77 (1H, m), 7.50 – 7.49 (2H, m), 6.12 (1H, s), 3.04 (3H, s).

Example 39

6-(2H-1,3-benzodioxol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2H-1,3-benzodioxol-5-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.42 – 7.39 (1H, m), 7.36 – 7.35 (1H, m), 6.89 (1H, d, J = 8.0 Hz), 6.15 (1H, s), 6.02 (1H, s), 2.92 (3H, s).

Example 40

3-[2-amino-6-(methylamino)pyrimidin-4-yl]benzonitrile.

Prepared according to general procedure 2 from (3-cyanophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 226; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.15 (1H, s), 8.05 – 8.03 (1H, m), 7.95 – 7.92 (1H, m), 7.74 (1H, t, J = 8.5 Hz), 6.35 (1H, s), 3.02 (3H, s).

Example 41

N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}acetamide.

Prepared according to general procedure 2 from (3-acetamidophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 (1H, s), 7.56 – 7.52 (2H, m), 7.45 – 7.43 (1H, m), 6.31 (1H, s), 3.06 (3H, s), 2.19 (3H, s).

Example 42

4-N-methyl-6-[4-(morpholine-4-sulfonyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [4-(morpholine-4-sulfonyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 350; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.99 (4H, s), 6.42 (1H, s), 3.76 – 3.72 (4H, m), 3.07 (3H, s), 3.06 – 3.03 (4H, m).

Example 43

6-(4-methanesulfonylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methanesulfonyl-phenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 279; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 – 8.17 (2H, m), 8.00 – 7.97 (2H, m), 6.41 (1H, s), 3.22 (3H, s), 3.08 (3H, s).

Example 44

4-N-methyl-6-[3-(morpholine-4-carbonyl)phenyl]pyrimidine-2,4-diamine. Prepared according to general procedure 2 from [3-(morpholine-4-carbonyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 314; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.00 – 7.96 (1H, m), 7.92 (1H, s), 7.57 (1H, t, J = 7.8 Hz), 7.52 (1H, dt, J = 7.8 and 1.4 Hz), 6.27 (1H, s), 3.79 – 3.50 (8H, m), 2.94 (3H, s).

Example 45

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-(furan-2-ylmethyl)benzamide. Prepared according to general procedure 2 from {4-[(furan-2-ylmethyl)carbamoyl]phenyl}boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 324; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.93 – 7.90 (4H, m), 7.46 – 7.44 (1H, m), 6.39 – 6.37 (1H, m), 6.34 – 6.32 (1H, m), 6.28 (1H, s), 4.60 (2H, s), 2.94 (3H, s).

Example 46

N-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanesulfonamide. Prepared according to general procedure 2 from (4-methanesulfon-amidophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 294; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.72 – 7.70 (2H, m), 7.43 – 7.40 (2H, m), 6.29 (1H, s), 3.06 (3H, s), 3.03 (3H, s).

Example 47

N-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}acetamide. Prepared according to general procedure 2 from (4-acetamidophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.82 – 7.80 (2H, m), 7.75 – 7.73 (2H, m), 6.31 (1H, s), 3.03 (3H, s), 2.18 (3H, d, J = 2.5 Hz).

Example 48

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-N'-hydroxy-benzamidine

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzonitrile (intermediate 53) (1.0 equiv.) and hydroxylamine (2.0 equiv.) was stirred at reflux in ethanol for 3 h. The mixture was then purified by preparative LC. LCMS $[M+H]^+$ 397. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.66 - 7.70 (m, 2 H), 7.58 - 7.62 (m, 1 H), 7.53 - 7.58 (m, 2 H), 7.30 - 7.38 (m, 2 H), 6.02 (s, 1 H), 3.82 (t, *J*=7.3 Hz, 2 H), 3.09 (t, *J*=7.4 Hz, 2 H), 2.37 (s, 3 H).

Example 49

6-(6-methoxypyridin-3-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (6-methoxypyridin-3-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 232; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.57 (1H, s), 8.03 (1H, d, J = 7.3 Hz), 6.98 (1H, d, J = 7.3 Hz), 6.30 (1H, s), 4.02 (3H, s), 3.07 (3H, s).

Example 50

6-(2-fluoro-4-phenylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-fluoro-4-phenylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 295; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 – 7.61 (5H, m), 7.54 – 7.44 (3H, m), 6.41 (1H, s), 6.30 (1H, s), 3.06 (3H, s).

Example 51

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzonitrile.

Prepared according to general procedure 2 from (4-cyanophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 226; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.03 (2H, d, J = 8.2 Hz), 7.84 – 7.80 (2H, m), 6.29 (1H, s), 2.93 (3H, s).

Example 52

4-N-methyl-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (quinolin-5-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 252; ^1H NMR (400

MHz, CD_3OD) δ ppm 8.98 (1H, dd, J = 4.2 and 1.9 Hz), 8.49 (1H, d, J = 8.6 Hz), 8.26 (1H, d, J = 8.6 Hz), 7.95 – 7.91 (1H, m), 7.82 (1H, d, J = 7.2 Hz), 7.67 (1H, dd, J = 8.6 and 4.2 Hz), 6.23 (1H, s), 3.08 (3H, s).

Example 53

6-(4-chlorophenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 – 7.73 (2H, m), 7.64 – 7.62 (2H, m), 6.36 (1H, s), 6.02 – 5.92 (1H, m), 5.33 – 5.31 (1H, m), 5.23 – 5.20 (1H, m), 4.18 – 4.16 (2H, m).

Example 54

6-(4-methoxyphenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257.

Example 55

6-(4-chlorophenyl)-4-N-cyclopentylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.60 (2H, d, J = 8.8 Hz), 7.51 – 7.49 (2H, m), 6.17 (1H, s), 4.36 (1H, s), 2.00 – 1.93 (2H, m), 1.73 – 1.65 (2H, m), 1.61 – 1.53 (2H, m), 1.50 – 1.43 (2H, m).

Example 56

4-N-cyclopentyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine and (4-methoxyphenyl)boronic acid. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.68 (2H, d, J = 9.2 Hz), 7.12 (2H, d, J = 9.2 Hz), 6.27 (1H, s), 4.47 (1H, q, J = 6.7 Hz), 3.89 (3H, s), 2.10 – 2.03 (2H, m), 1.82 – 1.79 (2H, m), 1.72 – 1.63 (2H, m), 1.62 – 1.53 (2H, m).

Example 57

4-N-cyclopentyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)-phenyl]boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.17 (1H, s), 8.08 (1H, d, J = 7.9 Hz), 7.74 (1H, d, J = 7.9 Hz), 7.65 (1H, t, J = 7.9 Hz), 6.28 (1H, s), 4.29 (1H, s), 2.09 – 1.99 (2H, m), 1.75 – 1.74 (2H, m), 1.71 – 1.62 (2H, m), 1.60 – 1.49 (2H, m).

Example 58

6-(4-chlorophenyl)-4-N-cyclobutylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 275; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 6.17 (1H, s), 4.42 (1H, s), 2.44 – 2.38 (2H, m), 2.02 – 1.94 (2H, m), 1.83 – 1.76 (2H, m).

Example 59

4-N-cyclobutyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 271; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.68 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 6.22 (1H, s), 4.64 (1H, q, J = 7.9 Hz), 3.90 (3H, s), 2.46 – 2.38 (2H, m), 2.12 – 2.01 (2H, m), 1.87 – 1.78 (2H, m).

Example 60

4-N-cyclobutyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 309; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.68 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 6.22 (1H, s), 4.64 (1H, q, J = 7.9 Hz), 3.90 (3H, s), 2.46 – 2.38 (2H, m), 2.12 – 2.01 (2H, m), 1.87 – 1.78 (2H, m).

Example 61

6-(2,3-dichlorophenyl)-4-N-pentylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from pentan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^1H NMR (400 MHz,

CD_3OD) δ ppm 7.80 – 7.78 (1H, m), 7.52 – 7.50 (2H, m), 6.12 (1H, s), 3.54 – 3.50 (2H, m), 1.69 – 1.65 (2H, m), 1.42 – 1.39 (4H, m), 0.98 – 0.95 (3H, m).

Example 62

4-N-cyclopropyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 295; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (1H, dd, J = 7.9 and 1.6 Hz), 7.41 (1H, dd, J = 7.9 and 1.6 Hz), 7.28 (1H, t, J = 7.9 Hz), 6.35 (1H, s), 5.21 (1H, s), 4.78 (2H, s), 2.63 – 2.47 (1H, m), 0.86 – 0.78 (2H, m), 0.64 – 0.57 (2H, m).

Example 63

4-N-tert-butyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from 2-methylpropan-2-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 311.

Example 64

4-N-cyclobutyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclobutanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 309; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.60 – 7.58 (1H, m), 7.37 – 7.34 (2H, m), 5.89 (1H, s), 4.46 (1H, s), 3.37 (2H, s), 2.43 – 2.35 (2H, m), 2.01 – 1.94 (2H, m), 1.80 – 1.72 (2H, m).

Example 65

4-N-cyclopentyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopentanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.62 – 7.56 (1H, m), 7.40 – 7.34 (2H, m), 5.93 (1H, s), 3.37 (1H, s), 2.09 – 1.98 (2H, m), 1.82 – 1.72 (2H, m), 1.71 – 1.61 (2H, m), 1.58 – 1.48 (2H, m).

Example 66

6-(2,3-dichlorophenyl)-4-N-ethylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from ethanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz,

CD_3OD) δ ppm 7.62 – 7.57 (1H, m), 7.40 – 7.35 (2H, m), 5.92 (1H, s), 3.44 – 3.36 (2H, m), 1.24 (3H, t, J = 7.1 Hz).

Example 67

6-(2,3-dichlorophenyl)-4-N-(oxolan-3-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from oxolan-3-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.63 – 7.58 (1H, m), 7.39 – 7.35 (2H, m), 5.98 (1H, s), 4.59 (1H, s), 4.02 – 3.94 (2H, m), 3.90 – 3.82 (1H, m), 3.73 – 3.67 (1H, m), 2.36 – 2.26 (1H, m), 1.99 – 1.89 (1H, m).

Example 68

6-(3,4-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3,4-dichlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.96 (1H, d, J = 2.0 Hz), 7.77 (1H, d, J = 8.5 Hz), 7.70 – 7.55 (2H, m), 6.35 (1H, s), 3.06 (3H, s).

Example 69

6-(4-tert-butylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-tert-butylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.77 (2H, d, J = 8.7 Hz), 7.53 – 7.48 (2H, m), 6.22 (1H, s), 2.93 (3H, s), 1.38 (9H, s).

Example 70

4-N-methyl-6-(4-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-methylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.73 (2H, d, J = 8.9 Hz), 7.28 (2H, d, J = 8.9 Hz), 6.20 (1H, s), 2.93 (3H, s), 2.41 (3H, s).

Example 71

6-(2,4-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4-dichlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ 7.57 (1H, d, J = 1.9 Hz), 7.48 – 7.41 (2H, m), 5.98 (1H, s), 2.92 (3H, s).

Example 72

4-N-methyl-6-(2,4,5-trifluorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4,5-trifluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.86 – 7.75 (1H, m), 7.31 – 7.24 (1H, m), 6.25 (1H, s), 2.91 (3H, s).

Example 73

6-(4-fluoro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-fluoro-2-methoxyphenyl)-boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.57 (1H, dd, J = 8.5 and 6.3 Hz), 6.89 (1H, dd, J = 11.4 and 2.5 Hz), 6.76 (1H, td, J = 8.5 and 2.5 Hz), 6.19 (1H, s), 3.87 (3H, s), 2.90 (3H, s).

Example 74

6-(5-chloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (5-chloro-2-methylphenyl)-boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.33 – 7.23 (3H, m), 5.85 (1H, s), 2.92 (3H, s), 2.32 (3H, s).

Example 75

6-(2,4-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4-difluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.88 – 7.79 (1H, m), 7.10 – 7.00 (2H, m), 6.19 (1H, d, J = 2.0 Hz), 2.92 (3H, s).

Example 76

6-(5-fluoro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 5 from (5-fluoro-2-methoxyphenyl)-boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.36 (1H, dd, J = 9.4 and 3.1 Hz), 7.15 – 7.04 (2H, m), 6.28 (1H, s), 3.85 (3H, s), 2.91 (3H, s).

Example 77
6-(2-chlorophenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 5 from (2-chlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 235; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.51 – 7.44 (1H, m), 7.42 – 7.36 (2H, m), 5.98 (1H, s), 2.92 (3H, s).

Example 78
6-(2,3-dichlorophenyl)-N4-[2-(3-methylsulfonylanilino)ethyl]pyrimidine-2,4-diamine
Step 1. N'-(3-methylsulfonylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-3-methylsulfonyl-benzene.
Step 2. The title compound was prepared according to general procedure 9 from intermediate 21 and N'-(3-methylsulfonylphenyl)ethane-1,2-diamine. $[M+H]^+$ 452. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.50 (dd, *J*=8.1, 1.7 Hz, 1 H), 7.36 - 7.40 (m, 1 H), 7.28 - 7.35 (m, 3 H), 7.25 (t, *J*=1.4 Hz, 1 H), 6.85 (d, *J*=0.9 Hz, 1 H), 5.97 (s, 1 H), 5.03 - 5.26 (m, 3 H), 4.70 (br. s., 1 H), 3.65 (q, *J*=6.1 Hz, 2 H), 3.44 (q, *J*=6.4 Hz, 2 H), 3.08 (s, 3 H).

Example 79
6-(4-methoxy-3-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from (4-methoxy-3-methylphenyl)-boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.72 – 7.62 (2H, m), 6.99 (1H, d, J = 8.3 Hz), 6.18 (1H, s), 3.91 (3H, s), 2.94 (3H, s), 2.28 (3H, s).

Example 80
6-(3-chloro-4-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from (3-chloro-4-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^{1}H NMR

(400 MHz, CD_3OD) δ ppm 8.05 – 7.99 (1H, m), 7.87 – 7.79 (1H, m), 7.33 (1H, t, J = 8.2 Hz), 6.23 (1H, s), 2.94 (3H, s).

Example 81

4-N-methyl-6-[4-(trifluoromethoxy)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [4-(trifluoromethoxy)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.98 – 7.92 (2H, m), 7.38 – 7.32 (2H, m), 6.23 (1H, s), 2.93 (3H, s).

Example 82

6-(3-fluoro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-fluoro-4-methoxyphenyl)-boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.97 – 7.60 (2H, m), 7.21 – 7.12 (1H, m), 6.20 (1H, s), 3.95 (3H, s), 2.94 (3H, s).

Example 83

6-(3,4-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3,4-difluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.86 – 7.77 (1H, m), 7.74 – 7.66 (1H, m), 7.40 – 7.30 (1H, m), 6.23 (1H, s), 2.94 (3H, s).

Example 84

4-N-methyl-6-[4-(propan-2-yloxy)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [4-(propan-2-yloxy)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259.

Example 85

6-[2-fluoro-3-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-fluoro-3-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.98 (1H, t, J =

7.0 Hz), 7.87 (1H, t, J = 7.0 Hz), 7.52 (1H, t, J = 8.0 Hz), 6.27 (1H, d, J = 1.5 Hz), 3.00 (3H, s).

Example 86

6-(2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,3-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.24 – 7.18 (1H, m), 7.17 – 7.05 (2H, m), 5.82 (1H, s), 2.92 (3H, s), 2.35 (3H, s), 2.22 (3H, s).

Example 87

6-(3-chloro-2-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-chloro-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.71 – 7.65 (1H, m), 7.58 – 7.53 (1H, m), 7.30 – 7.22 (1H, m), 6.18 (1H, d, J = 2.1 Hz), 2.93 (3H, s).

Example 88

6-(4-chloro-3-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-chloro-3-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.73 – 7.65 (2H, m), 7.62 – 7.55 (1H, m), 6.34 (1H, s), 3.03 (3H, s).

Example 89

4-N-methyl-6-[2-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-(trifluoromethyl)-phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.80 (1H, d, J = 8.1 Hz), 7.70 (1H, t, J = 7.7 Hz), 7.61 (1H, t, J = 7.7 Hz), 7.48 (1H, d, J = 8.1 Hz), 5.88 (1H, s), 2.92 (3H, s).

Example 90

4-N-methyl-6-(1-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (1-methyl-1H-indazol-4-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.42 (1H, s), 7.69 – 7.63 (1H, m), 7.60 – 7.50 (2H, m), 6.33 (1H, s), 4.14 (3H, s), 2.97 (3H, s).

Example 91

6-[2-chloro-3-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from [2-chloro-3-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 303; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.90 – 7.85 (1H, m), 7.71 – 7.66 (1H, m), 7.62 – 7.55 (1H, m), 5.95 (1H, s), 2.94 (3H, s).

Example 92

6-(2-chloro-3-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from (2-chloro-3-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.46 – 7.38 (1H, m), 7.35 – 7.28 (2H, m), 5.98 (1H, s), 2.93 (3H, s).

Example 93

6-(2,3-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from (2,3-difluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.58 – 7.51 (1H, m), 7.34 – 7.31 (1H, m), 7.29 – 7.22 (1H, m), 6.20 (1H, s), 2.93 (3H, s).

Example 94

6-(3-chloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.
Prepared according to general procedure 6 from (3-chloro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.47 – 7.41 (1H, m), 7.27 – 7.21 (2H, m), 5.85 (1H, s), 2.93 (3H, s), 2.36 (3H, s).

Example 95

6-(2,3-dichlorophenyl)-4-N,5-dimethylpyrimidine-2,4-diamine.

Step 1: 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine was prepared according to general procedure 2 from 4,6-dichloro-5-methylpyrimidin-2-amine and (2,3-dichlorophenyl)boronic acid (and using DMF instead of dioxane).

Step 2: 6-(2,3-dichlorophenyl)-4-N,5-dimethylpyrimidine-2,4-diamine was prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine (prepared in step 1 above). LCMS $[M+H]^+$ 283; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.62 (1H, dd, J = 7.9 and 1.9 Hz), 7.41 (1H, t, J = 7.9 Hz), 7.27 (1H, dd, J = 7.9 and 1.9 Hz), 3.01 (3H, s), 1.71 (3H, s).

Example 96

4-N-cyclopropyl-6-(2,3-dichlorophenyl)-5-methylpyrimidine-2,4-diamine.

Was prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine (prepared in example 95, step 1 above). LCMS $[M+H]^+$ 309; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.83 (1H, dd, J = 7.7 and 1.2 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.48 (1H, dd, J = 7.8 and 1.2 Hz), 3.17 -3.09 (1H, m), 1.79 (3H, s), 0.96 – 0.90 (2H, m), 0.82 – 0.75 (2H, m).

Example 97

6-(7-chloro-2H-1,3-benzodioxol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 279; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.11 (1H, s), 7.04 (1H, s), 6.13 (2H, s), 6.10 (1H, s), 3.04 (3H, s).

Example 98

6-(2,3-dichloro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Step 1: 4-chloro-6-(2,3-dichloro-5-methoxyphenyl)pyrimidin-2-amine was prepared according to general procedure 2 from 4,6-dichloropyrimidin-2-amine and 2,3-dichloro-4-methoxyphenyl)boronic acid.

Step 2: Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichloro-5-methoxyphenyl)pyrimidin-2-amine (prepared in step 1

above). LCMS $[M+H]^+$ 299; ^1H NMR (400 MHz, CD_3OD) δ 7.49 (1H, d, J = 8.6 Hz), 7.24 (1H, d, J = 8.6 Hz), 6.11 (1H, s), 4.01 (3H, s), 3.09 (3H, s).

Example 99

6-(2,3-dichloro-5-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,3-dichloro-5-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 299; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.38 (1H, d, J = 2.9 Hz), 7.12 (1H, d, J = 2.9 Hz), 6.13 (1H, s), 3.88 (3H, s), 3.05 (3H, s).

Example 100

4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenol.

Prepared according to general procedure 6 from (4-hydroxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 217; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.69 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 6.15 (1H, s), 4.59 (1H, s), 2.93 (3H, s).

Example 101

{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol.

Prepared according to general procedure 6 from [3-(hydroxymethyl) phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 (1H, s), 7.76 – 7.70 (1H, m), 7.45 – 7.41 (2H, m), 6.22 (1H, s), 4.68 (2H, s), 2.92 (3H, s).

Example 102

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzoic acid.

Prepared according to general procedure 6 from 4-(dihydroxyboranyl)benzoic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245.

Example 103

methyl 4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzoate.

Prepared according to general procedure 6 from [4-(methoxycarbonyl)-phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.12 – 8.06 (2H, m), 7.95 (2H, d, J = 8.2 Hz), 6.28 (1H, s), 3.94 (3H, s), 2.93 (3H, s).

Example 104

6-[3-chloro-4-(morpholine-4-carbonyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [3-chloro-4-(morpholine-4-carbonyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 348; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.90 (1H, d, J = 1.8 Hz), 7.75 (1H, dd, J = 7.9 and 1.8 Hz), 7.59 (1H, d, J = 7.9 Hz), 6.35 (1H, s), 3.85 – 3.74 (6H, m), 3.69 – 3.60 (2H, m), 3.04 (3H, s).

Example 105

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2,3-dichlorophenol.

Prepared according to general procedure 6 from 2,3-dichloro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.32 (1H, d, J = 8.7 Hz), 7.04 (1H, d, J = 8.7 Hz), 6.09 (1H, s), 3.04 (3H, s).

Example 106

methyl (2E)-3-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoate.

Prepared according to general procedure 6 from {4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.82 (4H, s), 7.76 (1H, d, J = 16.0 Hz), 6.69 (1H, d, J = 16.0 Hz), 6.36 (1H, s), 3.83 (3H, s), 3.04 (3H, s).

Example 107

methyl (2E)-3-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoate.

Prepared according to general procedure 6 from {3-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.99 – 7.95 (1H, m), 7.92 – 7.86 (1H, m), 7.83 – 7.73 (2H, m), 7.69 – 7.63 (1H, m), 6.72 (1H, d, J = 16.0 Hz), 6.37 (1H, s), 3.83 (3H, s), 3.07 (3H, s).

Example 108

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzaldehyde.

Prepared according to general procedure 6 from (4-formylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229.

Example 109

1-(4-(2-Amino-6-(methylamino)pyrimidin-4-yl)phenyl)ethanone.

Prepared according to general procedure 6 from (4-acetylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 243; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.22 – 8.15 (2H, m), 7.88 – 7.82 (2H, m), 6.38 (1H, s), 3.05 (3H, s), 2.67 (3H, s).

Example 110

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-methylbenzamide.

Prepared according to general procedure 6 from [4-(methylcarbamoyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.02 (2H, d, J = 8.5 Hz), 7.83 (2H, d, J = 8.5 Hz), 6.38 (1H, s), 3.06 (3H, s), 2.97 (3H, s).

Example 111

6-(4-ethenylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-ethenylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine.

LCMS $[M+H]^+$ 227; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 – 7.63 (4H, m), 6.84 (1H, dd, J = 17.5 and 10.7 Hz), 6.34 (1H, s), 5.98 (1H, d, J = 17.5 Hz), 5.43 (1H, d, J = 10.7 Hz), 3.06 (3H, s).

Example 112

6-(2,3-dimethylphenyl)-4-N-[2-(piperidin-1-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(piperidin-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 326.

Example 113

6-(2,3-dimethylphenyl)-4-N-[2-(morpholin-4-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(morpholin-4-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 328.

Example 114

4-N-cyclopropyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.42 – 7.31 (1H, m), 7.29 – 7.12 (2H, m), 6.44 (0.3 H, s), 5.95 (0.7 H, s), 3.13. (0.7H, s), 2.68 (0.3H, s), 2.36 (3H, s), 2.25 (3H, s), 0.95 – 0.79 (2H, m), 0.72 – 0.55 (2H, m).

Example 115

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-(4-methylphenyl)benzamide.

Step 1: A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (48 mg, 0.30 mmol), 3-(dihydroxyboranyl)benzoic acid (60 mg, 0.36 mmol), K_2CO_3 (104 mg, 0.75 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (17 mg, 0.015 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C for 15 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 245.

Step 2: To a mixture of 3-(2-amino-6-(methylamino)pyrimidin-4-yl)benzoic acid (50 mg, 0.47 mmol) and p-toluidine (150 mg, 1.4 mmol) in DMF (2.5 mL) were added HATU (266 mg, 0.70 mmol) and NEt_3 (200 µL, 1.4 mmol). The mixture was stirred at rt overnight. The crude reaction mixture was purified by HPLC. LCMS $[M+H]^+$ 334.

Example 116

6-(1H-indol-3-yl)-4-N-methylpyrimidine-2,4-diamine.

To a solution of 4-N-methyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine (1 equiv.; prepared in example 23) in MeOH (2 mL) was added 10% NaOH (1 mL). The reaction mixture was heated at 50 °C overnight and the crude product was purified by HPLC. LCMS $[M+H]^+$ 240; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.04 (1H, d, J = 7.7 Hz), 7.82 (1H, s), 7.46 – 7.36 (1H, m), 7.21 – 7.09 (2H, m), 6.29 (1H, s), 2.92 (3H, s).

Example 117

6-phenyl-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from phenylboronic acid and 6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 291; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.83 – 7.73 (2H, m), 7.47 – 7.37 (3H, m), 7.31 – 7.22 (4H,

m), 7.21 – 7.15 (1H, m), 6.17 (1H, s), 3.60 (2H, t, J = 7.3 Hz), 2.91 (2H, t, J = 7.3 Hz).

Example 118

6-(2,3-dimethylphenyl)-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 319; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.31 – 7.23 (4H, m), 7.21 – 7.15 (2H, m), 7.10 (1H, t, J = 7.0 Hz), 7.05 (1H, d, J = 7.0 Hz), 5.77 (1H, s), 3.64 – 3.50 (2H, m), 2.90 (2H, t, J = 7.6 Hz), 2.31 (3H, s), 2.19 (3H, s).

Example 119

6-(3-chlorophenyl)-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285.

Example 120

6-(3-chloro-2-methoxypyridin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chloro-2-methoxypyridin-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 266.

Example 121

4-(2,3-dimethylphenyl)-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 equiv.) in DMF/water (9:1) is added 2,3-dimethylphenylboronic acid (8.9 mg, 0.060 mmol, 1.1 equiv.), Na_2CO_3 (11.5 mg, 0.11 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (3.1 mg, 0.002 mmol, 0.05 equiv.). The mixture is heated at 120 ºC in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.05 (1H, br s), 8.88 (1H, br s), 7.37 (1H, d, J = 6.9 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.17 (1H, d, J = 6.3 Hz), 3.34 – 3.32 (2H, m), 2.32 (3H, s), 2.28 – 2.26 (2H, m), 2.09 (3H, s), 1.76 – 1.74 (2H, m).

Example 122

4-(2,3-dichlorophenyl)-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 equiv.) in DMF/water (9:1) is added 2,3-dichlorophenylboronic acid (11.3 mg, 0.060 mmol, 1.1 equiv.), Na_2CO_3 (11.5 mg, 0.11 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (3.1 mg, 0.002 mmol, 0.05 equiv.). The mixture is heated at 120 ºC in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS $[M+H]^+$ 295.

Example 123

4-[1-(benzenesulfonyl)-1H-indol-3-yl]-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 equiv.) in DMF/water (9:1) is added (1-(phenylsulfonyl)-1H-indol-3-yl)boronic acid (18.0 mg, 0.060 mmol, 1.1 equiv.), Na_2CO_3 (11.5 mg, 0.11 mmol, 2 equiv.) and $Pd(PPh_3)_4$ (3.1 mg, 0.002 mmol, 0.05 equiv.). The mixture is heated at 120 ºC in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS $[M+H]^+$ 406; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.03 (1H, br s), 8.03 (1H, br s), 8.36 (1H, s), 8.09 (2H, dd, J = 8.6 Hz and 1.2 Hz), 8.04 (1H, d, J = 8.3 Hz), 7.78 – 7.76 (1H, m), 7.68 – 7.66 (2H, m), 7.61 (1H, d, J = 7.8 Hz), 7.48 (1H, ddd, J = 8.4 Hz, 7.3 Hz and 1.1 Hz), 7.38 (1H, ddd, J = 8.0 Hz, 7.2 Hz and 1.0 Hz), 3.38 – 3.36 (2H, m), 2.48 – 2.46 (2H, m), 1.76 – 1.74 (2H, m).

Example 124

6-(3,5-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3,5-difluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$237.

Example 125

6-(2,3-dimethylphenyl)-4-N-[2-(4-methoxyphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(4-methoxyphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 349.

Example 126

6-(2,3-dimethylphenyl)-4-N-[2-(2-methoxyphenyl)ethyl]pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 2-(2-methoxyphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 349.

Example 127
6-(2,3-dimethylphenyl)-4-N-[2-(4-methylphenyl)ethyl]pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 2-(4-methylphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 128
4-N-[2-(4-chlorophenyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 353.

Example 129
6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-2-yl)ethyl]pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 2-(pyridin-2-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 320.

Example 130
6-(2,3-dimethylphenyl)-4-N-(2-phenylpropyl)pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 2-phenylpropan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 131
6-(2,3-dimethylphenyl)-4-N-(3-phenylpropyl)pyrimidine-2,4-diamine. Prepared according to general procedure 7 from 3-phenylpropan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 132
6-(2,3-dimethylphenyl)-4-N-(2-phenoxyethyl)pyrimidine-2,4-diamine. Prepared according to general procedure 7 from (2-aminoethoxy)benzene and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 335.

Example 133

6-(2,3-dimethylphenyl)-4-N-[2-(phenylamino)ethyl]pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from N-(2-aminoethyl)aniline and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 334.

Example 134
6-(2,3-dimethylphenyl)-4-N-[2-(1H-indol-3-yl)ethyl]pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from 2-(1H-indol-3-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 358.

Example 135
6-(2,3-dimethylphenyl)-4-N-pentylpyrimidine-2,4-diamine.
Prepared according to general procedure 7 from pentan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 285.

Example 136
1-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)imidazolidin-2-one.
Prepared according to general procedure 7 from 1-(2-aminoethyl)imidazolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 327.

Example 137
1-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.
Prepared according to general procedure 7 from 1-(3-aminopropyl)pyrrolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340.

Example 138
4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2,6-dimethylphenol.
Prepared according to general procedure 6 from (4-hydroxy-3,5-dimethylphenyl)boronic acid. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.44 (2H, s), 6.12 (1H, s), 2.91 (3H, s), 2.27 (6H, s).

Example 139
4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-methoxyphenol.
Prepared according to general procedure 6 from (4-hydroxy-3-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

$[M+H]^+$ 247; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.46 (1H, s), 7.33 (1H, d, J = 8.4 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.17 (1H, s), 3.34 (3H, s), 2.92 (3H, s).

Example 140

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-fluorophenol.

Prepared according to general procedure 6 from (3-fluoro-4-hydroxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 235.

Example 141

5-[2-amino-6-(methylamino)pyrimidin-4-yl]pyridin-2-ol.

Prepared according to general procedure 6 from (6-hydroxypyridin-3-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 218; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.99 (1H, s), 7.86 (1H, d, J = 9.6 Hz), 6.68 (1H, dd, J = 9.6 and 0.4 Hz), 6.21 (1H, s), 3.04 (3H, s).

Example 142

{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol.

Prepared according to general procedure 6 from [4-(hydroxymethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.79 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.4 Hz), 6.21 (1H, s), 4.65 (2H, s), 2.91 (3H, s).

Example 143

4-N-methyl-6-(2-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.29 – 7.23 (4H, m), 5.83 (1H, s), 2.90 (3H, s), 2.33 (3H, s).

Example 144

6-[1-(4-chlorobenzenesulfonyl)-1H-indol-3-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-chlorobenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 414; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.15 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 8.04 (1H, d, J = 8.0 Hz), 8.00 – 7.98 (2H, m), 7.57 – 7.55 (2H, m), 7.41 (1H,

td, J = 8.4 and 1.2 Hz), 7.35 (1H, td, J = 8.0 and 0.8 Hz), 6.28 (1H, s), 2.29 (3H, s).

Example 145

4-N-methyl-6-(4-methyl-1H-indazol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-methyl-1H-indazol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255.

Example 146

4-N-methyl-6-(6-methyl-1H-indazol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (6-methyl-1H-indazol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.12 (1H, d, J = 0.8 Hz), 7.88 (1H, s), 7.56 (1H, d, J = 0.8 Hz), 6.09 (1H, s), 3.07 (3H, s), 2.50 (3H, d, J = 0.8 Hz).

Example 147

4-N-methyl-6-(3-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-methylphenyl)boronic acid. LCMS $[M+H]^+$ 215; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.56 (1H, s), 7.51 – 7.47 (3H, m), 6.32 (1H, s), 3.06 (3H, s), 2.47 (3H, s).

Example 148

6-(1H-indol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (1H-indol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 240; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.00 (1H, dd, J = 1.6 and 0.4 Hz), 7.59 (1H, td, J = 8.4 and 0.8 Hz), 7.47 (1H, dd, J = 8.4 and 1.6 Hz), 7.42 (1H, d, J = 3.2 Hz), 6.63 (1H, dd, J = 3.2 and 1.2 Hz), 6.35 (1H, s), 3.06 (3H, s).

Example 149

6-(3-chloropyridin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-chloropyridin-4-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 236; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.83 (1H, s), 8.71 (1H, d, J = 5.2 Hz), 7.62 (1H, d, J = 4.8 Hz), 6.24 (1H, s), 3.07 (3H, s).

Example 150

{5-[2-amino-6-(methylamino)pyrimidin-4-yl]pyridin-2-yl}methanol.

Prepared according to general procedure 6 from [6-(hydroxymethyl)pyridin-3-yl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 232.

Example 151

4-N-cyclobutyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.20 (1H, d, J = 7.2 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.08 (1H, d, J = 7.2 Hz), 5.77 (1H, s), 4.44 (1H, br s), 2.44 – 2.36 (2H, m), 2.34 (3H, s), 2.21 (3H, s), 2.04 – 1.94 (m, 2H), 1.82 – 1.73 (m, 2H).

Example 152

4-N-cyclobutyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 434; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.39 (1H, s), 8.09 (1H, d, J = 8.4 Hz), 7.96 – 7.94 (2H, m), 7.84 (1H, d, J = 8.0 Hz), 7.50 (1H, td, J = 7.2 and 0.8 Hz), 7.35 (1H, td, J = 7.2 and 0.8 Hz), 7.41 – 7.39 (2H, m), 6.44 (1H, s), 4.66 (1H, quintet, J = 8.4 Hz), 2.47 – 2.41 (2H, m), 2.39 (3H, s), 2.14 – 2.04 (2H, m), 1.89 – 1.82 (2H, m).

Example 153

4-N-cyclopentyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 7.2 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 1.6 Hz), 5.81 (1H, s), 4.25 (1H, br s), 2.33 (3H, s), 2.22 (3H, s), 2.06 – 2.00 (2H, m), 1.81 – 1.74 (2H, m), 1.71 – 1.63 (2H, m), 1.58 – 1.51 (2H, m).

Example 154

4-N-cyclopentyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.38 (1H, s), 8.10 (1H, d, J = 8.4 Hz), 7.96 – 7.94 (2H, m), 7.84 (1H, d, J = 8.0 Hz), 7.50 (1H, td, J = 7.2 and 1.2 Hz), 7.42 (1H, td, J = 7.2 and 0.8 Hz), 7.41 – 7.39 (2H, m), 6.48 (1H, s), 4.51 (1H, quintet, J = 6.8 Hz), 2.39 (3H, s), 2.14 – 2.05 (2H, m), 1.84 – 1.78 (2H, m), 1.75 – 1.66 (2H, m), 1.63 – 1.57 (2H, m).

Example 155

4-N-methyl-6-{1-[4-(trifluoromethyl)benzenesulfonyl]-1H-indol-3-yl}pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from {1-[4-(trifluoromethyl)benzenesulfonyl]-1H-indol-3-yl}boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.19 (2H, d, J = 8.4 Hz), 8.16 (1H, s), 8.08 – 8.04 (2H, m), 7.84 (2H, d, J = 8.4 Hz), 7.41 (1H, td, J = 7.6 and 0.8 Hz), 7.34 (1H, td, J = 8.0 and 0.8 Hz), 6.26 (1H, s), 2.92 (s, 3H).

Example 156

4-N-cyclohexyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 297; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 7.2 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 1.6 Hz), 5.78 (1H, s), 3.82 (1H, br s), 2.33 (3H, s), 2.21 (3H, s), 2.03 – 1.99 (2H, m), 1.83 – 1.78 (2H, m), 1.71 – 1.66 (1H, m), 1.48 – 1.37 (2H, m), 1.31 – 1.21 (3H, m).

Example 157

4-N-cyclohexyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 462; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.36 (1H, s), 8.08 (1H, d, J

= 8.0 Hz), 7.95 – 7.93 (2H, m), 7.83 (1H, d, J = 8.0 Hz), 7.48 (1H, td, J = 7.2 and 0.8 Hz), 7.41 (1H, td, J = 8.0 and 1.2 Hz), 7.40 – 7.38 (2H, m), 6.46 (1H, s), 4.11 – 4.05 (1H, m), 2.38 (3H, s), 2.04 – 2.00 (2H, m), 1.86 – 1.82 (2H, m), 1.72 – 1.68 (1H, m), 1.48 – 1.26 (5H, m).

Example 158

6-(2,3-dimethylphenyl)-4-N-ethylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 243; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 7.2 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 1.2 Hz), 5.80 (1H, s), 3.41 – 3.36 (2H, m), 2.33 (3H, s), 2.21 (3H, s), 1.23 (3H, t, J = 7.2 Hz).

Example 159

4-N-ethyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 408; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.12 (1H, s), 8.05 – 8.01 (2H, m), 7.87 – 7.85 (2H, m), 7.37 (1H, td, J = 7.2 and 1.2 Hz), 7.34 – 7.32 (2H, m), 7.30 (1H, td, J = 8.0 and 1.2 Hz), 6.26 (1H, s), 3.39 (2H, q, J = 7.2 Hz), 2.34 (3H, s), 1.24 (3H, t, J = 7.2 Hz).

Example 160

4-N-tert-butyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 271; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.18 (1H, d, J = 7.2 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.07 (1H, dd, J = 7.6 and 1.6 Hz), 5.81 (1H, s), 2.33 (3H, s), 2.21 (3H, s), 1.49 (9H, s).

Example 161

4-N-tert-butyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 436; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.36 (1H, s), 8.08 (1H, d, J

= 8.4 Hz), 7.95 – 7.93 (2H, m), 7.84 (1H, d, J = 7.6 Hz), 7.48 (1H, td, J = 7.2 and 1.2 Hz), 7.40 (1H, td, J = 8.4 and 1.2 Hz), 7.40 – 7.38 (2H, m), 6.52 (1H, s), 2.38 (3H, s), 1.54 (9H, s).

Example 162

6-(2,3-dimethylphenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.36 (1H, d, J = 7.2 Hz), 7.25 (1H, t, J = 7.6 Hz), 7.19 (1H, d, J = 7.2 Hz), 5.96 (1H, s), 4.39 (1H, septet, J = 6.4 Hz), 2.37 (3H, s), 2.26 (3H, s), 1.29 (3H, s), 1.27 (3H, s).

Example 163

6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 422; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.12 (1H, s), 8.05 – 8.02 (2H, m), 7.89 – 7.86 (2H, m), 7.40 – 7.30 (4H, m), 6.25 (1H, s), 4.19 (1H, br s), 2.36 (3H, s), 1.26 (3H, s), 1.24 (3H, s).

Example 164

4-N-(cyclopropylmethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269.

Example 165

4-N-(cyclopropylmethyl)-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 434; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.14 (1H, s), 8.06 – 8.02 (2H, m), 7.88 – 7.86 (2H, m), 7.40 – 7.30 (5H, m), 6.31 (1H, s), 3.25 (2H, d, J = 6.8 Hz), 1.14 – 1.11 (1H, m), 0.57 – 0.55 (2H, m), 0.30 – 0.28 (2H, m).

Example 166

4-N-[(1R)-1-cyclopropylethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 6.8 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.09 (1H, dd, J = 7.6 and 1.2 Hz), 5.80 (1H, s), 3.58 (1H, br s), 2.34 (3H, s), 2.22 (3H, s), 1.28 (3H, d, J = 6.4 Hz), 0.99 – 0.92 (1H, m), 0.57 – 0.45 (2H, m), 0.44 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

Example 167

4-N-[(1R)-1-cyclopropylethyl]-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.37 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 7.95 – 7.93 (2H, m), 7.84 (1H, d, J = 7.6 Hz), 7.49 (1H, dt, J = 7.6 and 1.2 Hz), 7.42 (1H, dt, J = 8.0 and 0.8 Hz), 7.40 – 7.38 (2H, m), 6.47 (1H, s), 3.78 – 3.71 (1H, m), 2.38 (3H, s), 1.33 (3H, d, J = 6.8 Hz), 1.04 – 0.99 (1H, m), 0.64 – 0.57 (1H, m), 0.56 – 0.49 (1H, m), 0.47 – 0.41 (1H, m), 0.33 – 0.27 (1H, m).

Example 168

4-N-[(1S)-1-cyclopropylethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.18 (1H, d, J = 6.8 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.07 (1H, dd, J = 7.6 and 1.6 Hz), 5.78 (1H, s), 3.56 (1H, br s), 2.32 (3H, s), 2.20 (3H, s), 1.27 (3H, d, J = 6.4 Hz), 0.98 – 0.91 (1H, m), 0.56 – 0.43 (2H, m), 0.42 – 0.36 (1H, m), 0.27 – 0.21 (1H, m).

Example 169

4-N-[(1S)-1-cyclopropylethyl]-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-

2,4-diamine. LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.37 (1H, s), 8.09 (1H, d, J = 8.4 Hz), 7.96 – 7.94 (2H, m), 7.85 (1H, d, J = 8.0 Hz), 7.49 (1H, dt, J = 7.6 and 1.2 Hz), 7.42 (1H, dt, J = 8.0 and 1.2 Hz), 7.41 – 7.39 (2H, m), 6.47 (1H, s), 3.78 – 3.71 (1H, m), 2.39 (3H, s), 1.33 (3H, d, J = 6.8 Hz), 1.05 – 0.98 (1H, m), 0.63 – 0.58 (1H, m), 0.57 – 0.50 (1H, m), 0.48 – 0.42 (1H, m), 0.33 – 0.27 (1H, m).

Example 170

6-(1-benzofuran-3-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (1-benzofuran-3-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 241; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.27 (1H, s), 8.07 (1H, dd, J = 8.0 and 1.2 Hz), 7.58 – 7.56 (1H, m), 7.35 (2H, dt, J = 7.6 and 1.2 Hz), 6.32 (1H, s), 2.95 (3H, s).

Example 171

6-(2-chloro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-chloro-5-methylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.35 (1H, d, J = 8.0 Hz), 7.28 (1H, d, J = 2.0 Hz), 7.23 – 7.20 (1H, m), 5.97 (1H, s), 2.92 (3H, s), 2.38 (3H, s).

Example 172

6-(1-benzothiophen-3-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (1-benzothiophen-3-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ 8.27 (1H, d, J = 7.2 Hz), 7.97 – 7.94 (1H, m), 7.92 (1H, s), 7.45 (1H, dt, J = 7.2 and 1.6 Hz), 7.41 (1H, dt, J = 7.2 and 1.6 Hz), 6.20 (1H, s), 2.95 (3H, s).

Example 173

2-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}propan-2-ol.

Prepared according to general procedure 2 from [4-(2-hydroxypropan-2-yl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.82 – 7.80 (2H, m), 7.60 – 7.57 (2H, m), 6.23 (1H, s), 2.94 (3H, s), 1.58 (6H, s).

Example 174

6-(1H-indol-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (1H-indol-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 240; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.50 – 7.48 (1H, m), 7.38 (1H, dd, J = 7.6 and 0.8 Hz), 7.34 (1H, d, J = 3.2 Hz), 7.21 (1H, t, J = 7.6 Hz), 6.80 (1H, dd, J = 3.2 and 0.8 Hz), 6.31 (1H, s), 2.96 (3H, s).

Example 175

4-N-cyclohexyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclohexanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 337; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.63 – 7.61 (1H, m), 7.40 (1H, d, J = 2.0 Hz), 7.39 (1H, s), 5.93 (1H, s), 3.88 (1H, br s), 2.06 – 2.02 (2H, m), 1.86 – 1.81 (2H, m), 1.73 – 1.69 (1H, m), 1.50 – 1.40 (2H, m), 1.34 – 1.25 (3H, m).

Example 176

6-(2,3-dichlorophenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from propan-2-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 297; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.61 – 7.59 (1H, m), 7.38 (1H, d, J = 2.0 Hz), 7.37 (1H, s), 5.92 (1H, s), 4.17 (1H, br s), 1.25 (3H, s), 1.24 (3H, s).

Example 177

4-N-(cyclopropylmethyl)-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropylmethanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 309.

Example 178

4-N-[(1S)-1-cyclopropylethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from (1S)-1-cyclopropylethan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.61 – 7.59 (1H, m), 7.38 (1H, d, J = 2.0 Hz),

7.37 (1H, s), 5.92 (1H, s), 3.59 (1H, br s), 1.28 (3H, d, J = 6.8 Hz), 0.99 – 0.92 (2H, m), 0.53 – 0.48 (2H, m), 0.46 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

Example 179

4-N-[(1R)-1-cyclopropylethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 3 from (1R)-1-cyclopropylethan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.61 – 7.59 (1H, m), 7.38 (1H, d, J = 2.0 Hz), 7.37 (1H, s), 5.92 (1H, s), 3.59 (1H, br s), 1.28 (3H, d, J = 6.8 Hz), 0.99 – 0.92 (2H, m), 0.58 – 0.47 (2H, m), 0.46 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

Example 180

6-(2,3-dichlorophenyl)-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. Prepared according to general procedure 3 from 2,2-dimethylpropan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.61 – 7.58 (1H, m), 7.38 (1H, d, J = 2.0 Hz), 7.36 (1H, s), 6.01 (1H, s), 3.27 (2H, br s), 0.98 (9H, s).

Example 181

6-(2,3-dimethylphenyl)-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. Prepared according to general procedure 5 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.20 (1H, d, J = 6.8 Hz), 7.14 (1H, t, J = 7.6 Hz), 7.10 (1H, dd, J = 7.6 and 1.6 Hz), 5.90 (1H, s), 2.34 (3H, s), 2.22 (3H, s), 1.00 (9H, s).

Example 182

4-N-(2,2-dimethylpropyl)-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.
Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 450; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.14 (1H, s), 8.08 (1H, d, J = 7.6), 8.04 (1H, dt, J = 8.0 and 1.2 Hz), 7.90 – 7.88 (2H, m), 7.39 (1H, td, J = 7.2 and 1.2 Hz), 7.37 – 7.34 (2H, m), 7.33 (1H, td, J = 7.2 and 1.2 Hz), 6.38 (1H, s), 3.27 (2H, s), 2.37 (3H, s), 1.02 (9H, s).

Example 183

6-(5-bromo-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-bromo-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 309; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.72 (1H, d, J = 2.4 Hz), 7.52 (1H, dd, J = 8.8 and 2.8 Hz), 7.04 (1H, d, J = 9.2 Hz), 6.25 (1H, s), 3.87 (3H, s), 2.91 (s, 3H).

Example 184

6-(2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.16 – 7.13 (2H, m), 7.11 (1H, s), 5.84 (1H, s), 2.92 (3H, s), 2.35 (3H, s), 2.29 (3H, s).

Example 185

4-N-methyl-6-[2-(trifluoromethyl)pyridin-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-(trifluoromethyl)pyridin-3-yl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 270.

Example 186

6-(3-chloro-2-methyl-phenyl)-N4-[2-(3-methylsulfonylanilino)ethyl]pyrimidine-2,4-diamine

Step 1. N'-(3-methylsulfonylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-3-methylsulfonyl-benzene.

Step 2. The title compound was prepared according to general procedure 9 from intermediate 24 and N'-(3-methylsulfonylphenyl)ethane-1,2-diamine. $[M+H]^+$ 432. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.37 (dd, *J*=7.3, 1.9 Hz, 1 H), 7.28 - 7.33 (m, 2 H), 7.20 - 7.24 (m, 1 H), 7.12 - 7.20 (m, 2 H), 6.82 (ddd, *J*=8.2, 2.5, 0.9 Hz, 1 H), 5.76 (s, 1 H), 5.18 (br. s., 3 H), 4.66 - 4.79 (m, 1 H), 3.62 (d, *J*=6.3 Hz, 2 H), 3.38 - 3.45 (m, 2 H), 3.05 - 3.08 (m, 3 H), 2.36 (s, 3 H).

Example 187

6-[4-(benzyloxy)-2-methylphenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [4-(benzyloxy)-2-methylphenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 321; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.47 – 7.46 (2H, m), 7.41 – 7.38 (2H, m), 7.35 – 7.32 (1H, m), 7.24 (1H, d, J = 8.4 Hz), 6.92 – 6.87 (2H, m), 5.84 (1H, s), 5.14 (2H, s), 2.91 (3H, s), 2.34 (3H, s).

Example 188

6-(4-methoxy-2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-methoxy-2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.08 (1H, s), 6.79 (1H, s), 5.83 (1H, s), 3.86 (3H, s), 2.91 (3H, s), 2.34 (3H, s), 2.19 (3H, s).

Example 189

4-N-methyl-6-(2,4,5-trimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,4,5-trimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 243; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.07 (1H, s), 7.03 (1H, s), 5.83 (1H, s), 2.91 (3H, s), 2.28 (9H, s).

Example 190

2-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-chlorobenzonitrile.

Prepared according to general procedure 6 from (5-chloro-2-cyanophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 260.

Example 191

6-(4,5-dichloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4,5-dichloro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.62 (1H, s), 7.61 (1H, s), 6.06 (1H, s), 3.04 (3H, s), 2.36 (3H, s).

Example 192

6-(2,5-dichloro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dichloro-4-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 299; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.52 (1H, s), 7.22 (1H, s), 6.03 (1H, s), 3.96 (3H, s), 2.92 (3H, s).

Example 193

6-(4-fluoro-2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 247; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.16 (1H, d, J = 8.0 Hz), 6.95 (1H, d, J = 10.8 Hz), 5.83 (1H, s), 2.91 (3H, s), 2.30 (3H, s), 2.27 (3H, s).

Example 194

4-N-methyl-6-[2-methyl-5-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-methyl-5-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.78 – 7.73 (2H, m), 7.61 (1H, d, J = 8.0 Hz), 6.08 (1H, s), 3.05 (3H, s), 2.46 (3H, s).

Example 195

6-[5-chloro-2-methyl-4-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [5-chloro-2-methyl-4-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 317; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.69 (1H, s), 7.53 (1H, s), 5.89 (1H, s), 2.93 (3H, s), 2.40 (3H, s).

Example 196

6-[2,5-bis(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2,5-bis(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 – 8.15 (2H, m), 8.10 (1H, s), 6.15 (1H, s), 3.08 (3H, s).

Example 197

6-(5-tert-butyl-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-tert-butyl-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.64 (1H, dd, J = 8.8 and 2.4 Hz), 7.51 (1H, s), 7.17 (1H, d, J = 8.8 Hz), 6.25 (1H, s), 3.94 (3H, s), 3.05 (3H, s), 1.37 (9H, s).

Example 198

6-[2-methoxy-5-(propan-2-yl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-methoxy-5-(propan-2-yl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.49 (1H, dd, J = 8.4 and 2.0 Hz), 7.39 (1H, s), 7.17 (1H, d, J = 8.8 Hz), 6.28 (1H, s), 3.95 (3H, s), 3.06 (3H, s), 2.98 (1H, sept, J = 6.8 Hz), 1.31 (3H, s), 1.30 (3H, s).

Example 199

6-[2-chloro-5-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-chloro-5-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 303; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.87 (1H, br s), 7.82 (1H, d, J = 2.0 Hz), 7.81 (1H, s), 6.14 (1H, s), 3.03 (3H, s).

Example 200

6-(2-fluoro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-fluoro-5-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 233; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.58 (1H, dd, J = 7.2 and 2.0 Hz), 7.28 – 7.25 (1H, m), 7.10 – 7.06 (1H, m), 6.02 (1H, d, J = 1.6 Hz), 2.94 (3H, s), 2.40 (3H, s).

Example 201

6-(5-chloro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 265; ^1H NMR (400 MHz, CD_3OD) δ 7.58 – 7.57 (1H, m), 7.56 (1H, d, J = 2.8 Hz), 7.23 (1H, d, J = 9.6 Hz), 6.27 (1H, s), 3.96 (3H, s), 3.05 (3H, s).

Example 202

6-(5-fluoro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-fluoro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 233; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.31 – 7.27 (1H, m), 7.08 – 7.04 (2H, m), 5.87 (1H, s), 2.94 (3H, s), 2.33 (3H, s).

Example 203

6-(2,5-dimethoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dimethoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.18 (1H, d, J = 3.2 Hz), 7.04 (1H, d, J = 9.2 Hz), 6.98 (1H, dd, J = 8.8 and 3.2 Hz), 6.27 (1H, s), 3.83 (6H, s), 2.93 (3H, s).

Example 204

6-(2-methoxy-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-methoxy-5-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ 7.36 (1H, s), 7.20 (1H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 6.20 (1H, s), 3.83 (3H, s), 2.91 (3H, s), 2.33 (3H, s).

Example 205

6-(2-chloro-5-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.54 – 7.50 (1H, m), 7.25 (1H, dd, J = 9.2 and 3.2 Hz), 7.19 (1H, td, J = 8.8 and 3.2 Hz), 6.01 (1H, s), 2.93 (3H, s).

Example 206

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-fluorobenzonitrile.

Prepared according to general procedure 6 from (5-cyano-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 244; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.26 (1H, dd, J = 6.8 and 2.0 Hz), 7.87 – 7.84 (1H, m), 7.45 – 7.40 (1H, m), 6.27 (1H, d, J = 2.0 Hz), 2.93 (3H, s).

Example 207

6-(2-chloro-5-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 265; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.39 (1H, d, J = 8.8 Hz), 7.02 (1H, d, J = 3.2 Hz), 6.98 (1H, dd, J = 8.8 and 3.2 Hz), 5.99 (1H, s), 3.84 (3H, s), 2.92 (3H, s).

Example 208

6-[5-fluoro-2-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [5-fluoro-2-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.87 – 7.83 (1H, m), 7.39 – 7.34 (1H, m), 7.25 (1H, dd, J = 9.2 and 2.8 Hz), 5.89 (1H, s), 2.92 (3H, s).

Example 209

6-(2,5-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dichlorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.51 – 7.49 (2H, m), 7.42 (1H, dd, J = 8.4 and 2.4 Hz), 6.01 (1H, s), 2.92 (3H, s).

Example 210

6-(5-chloro-2-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 – 7.23 (1H, m), 7.69 – 7.65 (1H, m), 7.40 (1H, m), 6.31 (1H, s), 3.07 (3H, s).

Example 211

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-methylbenzonitrile.

Prepared according to general procedure 6 from (5-cyano-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

$[M+H]^+$ 240; ^1H NMR (400 MHz, CD_3OD) δ 7.68 – 7.66 (2H, m), 7.48 (1H, d, J = 7.6 Hz), 5.88 (1H, s), 2.93 (3H, s), 2.44 (3H, s).

Example 212

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-methoxybenzonitrile.

Prepared according to general procedure 6 from (5-cyano-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 256; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.95 (1H, d, J = 2.4 Hz), 7.98 (1H, dd, J = 8.8 and 2.0 Hz), 7.27 (1H, d, J = 8.8 Hz), 6.26 (1H, s), 3.97 (3H, s), 2.92 (3H, s).

Example 213

6-(2-chloro-5-fluoro-4-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-fluoro-4-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 267; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.39 (1H, d, J = 6.8 Hz), 7.19 (1H, d, J = 9.6 Hz), 6.02 (1H, s), 2.92 (3H, s), 2.32 (3H, d, J = 1.6 Hz).

Example 214

6-(5-chloro-2-fluoro-4-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-2-fluoro-4-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 267; ^1H NMR (400 MHz, CD_3OD) δ 7.72 (1H, d, J = 6.8 Hz), 7.19 (1H, d, J = 11.2 Hz), 6.31(1H, s), 3.05 (3H, s), 2.48 (3H, s).

Example 215

6-(2-chloro-4-fluoro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-4-fluoro-5-methylphenyl)boronic acid. and 6-iodo-4-N-methylpyrimidine-2,4-diamine LCMS $[M+H]^+$ 267; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.36 (1H, d, J = 8.4 Hz), 7.23 (1H, d, J = 9.6 Hz), 5.96 (1H, s), 2.91 (3H, s), 2.29 (3H, d, J = 1.6 Hz).

Example 216

4-N-cyclopropyl-6-(4-fluoro-2,5-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 10.4 Hz), 6.03 (1H, s), 2.63 (1H, br s), 2.33 (3H, s), 2.28 (3H, s), 0.84 – 0.79 (2H, m), 0.60 – 0.56 (2H, m).

Example 217

4-N-cyclopropyl-6-(4-methoxy-2,5-dimethylphenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 2 from (4-methoxy-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285.

Example 218

4-N-cyclopropyl-6-(2,5-dimethylphenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 2 from (2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.30 – 7.28 (2H, m), 7.23 (1H, s), 6.00 (1H, s), 3.06 (1H, br s), 2.40 (3H, s), 2.36 (3H, s), 0.93 – 0.88 (2H, m), 0.69 – 0.66 (2H, m).

Example 219

6-(5-chloro-2-methylphenyl)-4-N-cyclopropylpyrimidine-2,4-diamine. Prepared according to general procedure 2 from (5-chloro-2-methylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 275; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.33 – 7.27 (3H, m), 6.05 (1H, s), 2.65 (1H, br s), 0.84 – 0.79 (2H, m), 0.60 – 0.56 (2H, m).

Example 220

6-(5-chloro-2-methylphenyl)-4-N-cyclobutylpyrimidine-2,4-diamine. Prepared according to general procedure 2 from (5-chloro-2-methylphenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.33 – 7.26 (3H, m), 5.81 (1H, s), 4.45 (1H, br s), 2.44 – 2.37 (2H, m), 2.32 (3H, s), 2.05 – 1.95 (2H, m), 1.83 – 1.74 (2H, m).

Example 221

6-(5-chloro-2-methylphenyl)-4-N-ethylpyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (5-chloro-2-methylphenyl)boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 263; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.51 – 7.46 (2H, m), 7.41 (1H, d, J = 8.4 Hz), 6.05 (1H, s), 3.57 (2H, q, J = 6.8 Hz), 2.37 (3H, s), 1.28 (3H, t, J = 7.2 Hz).

Example 222
6-(5-chloro-2-methylphenyl)-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (5-chloro-2-methylphenyl)boronic acid and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 373; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.32 – 7.26 (7H, m), 5.81 (1H, s), 3.64 – 3.60 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 2.31 (3H, s).

Example 223
4-N-[2-(4-chlorophenyl)ethyl]-6-(4-fluoro-2,5-dimethylphenyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 371; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.32 – 7.26 (4H, m), 7.14 (1H, d, J = 8.0 Hz), 6.94 (1H, d, J = 10.8 Hz), 5.79 (1H, s), 3.63 – 3.59 (2H, m), 2.92 (2H, t, J = 7.2 Hz), 2.30 (3H, s), 2.27 (3H, s).

Example 224
4-N-[2-(4-chlorophenyl)ethyl]-6-(2,5-dimethylphenyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from (2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 353; ^1H NMR (400 MHz, CD_3OD) δ 7.32 – 7.26 (4H, m), 7.16 – 7.09 (3H, m), 5.80 (1H, s), 3.61 (2H, t, J = 6.4 Hz), 2.92 (2H, t, J = 7.2 Hz), 2.35 (3H, s), 2.28 (3H, s).

Example 225
1-(3-{[2-amino-6-(quinolin-5-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.
Prepared according to general procedure 2 from (quinolin-5-yl)boronic acid and 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one.LCMS $[M+H]^+$

363; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.90 (1H, dd, J = 4.0 and 1.6 Hz), 8.64 (1H, d, J = 8.8 Hz), 8.12 (1H, d, J = 8.4 Hz), 7.88 – 7.84 (1H, m), 7.71 (1H, d, J = 7.2 Hz), 7.59 – 7.56 (1H, m), 6.07 (1H, s), 3.53 (2H, t, J = 6.8 Hz), 3.42 (4H, t, J = 6.8 Hz), 2.42 (2H, t, J = 8.0 Hz), 2.12 – 2.05 (2H, m), 1.93 – 1.86 (2H, m).

Example 226

6-(2-chloro-3-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 249; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.56 – 7.54 (1H, m), 7.42 – 7.37 (2H, m), 6.11 (1H, s), 3.05 (3H, s), 2.49 (3H, s).

Example 227

6-(2-chloro-3-methylphenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 275; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.56 (1H, d, J = 5.6 Hz), 7.42 – 7.39 (2H, m), 6.07 (1H, s), 3.09 (1H, br s), 2.50 (3H, s), 0.92 – 0.90 (2H, m), 0.68 (2H, br s).

Example 228

6-(2-chloro-3-methylphenyl)-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 373; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.57 – 7.55 (1H, m), 7.41 (1H, t, J = 7.6 Hz), 7.37 (1H, dd, J = 8.0 and 2.0 Hz), 7.34 – 7.28 (4H, m), 6.08 (1H, s), 3.79 (2H, t, J = 7.2 Hz), 2.97 (2H, t, J = 7.2 Hz), 2.49 (3H, s).

Example 229

1-(3-{[2-amino-6-(2-chloro-3-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

Prepared according to general procedure 3 from 1-(3-aminopropyl)pyrrolidin-2-one and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 360; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.57 – 7.55 (1H, m), 7.44 – 7.38 (2H, m), 6.13 (1H, s),3.55 (2H, t, J = 5.6 Hz), 3.52 (2H, t, J = 7.2 Hz), 3.41 (2H, t, J = 6.8

Hz), 2.49 (3H, s), 2.42 (2H, t, J = 8.0 Hz), 2.09 (2H, quintet, J = 7.6 Hz), 1.92 (2H, quintet, J = 7.2 Hz).

Example 230

4-N-cyclopropyl-6-(1H-indol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 266; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.67 (1H, d, J = 7.6 Hz), 7.50 (1H, s), 7.33 (2H, d, J = 7.2 Hz), 6.71 (1H, s), 6.43 (1H, s), 3.10 (1H, br s), 0.92 (2H, br s), 0.69 (2H, br s).

Example 231

4-N-[2-(4-chlorophenyl)ethyl]-6-(1H-indol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 364; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.67 – 7.66 (1H, m), 7.52 – 7.46 (1H, m), 7.35 – 7.29 (6H, m), 6.86 (1H, s), 6.44 (1H, s), 3.80 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 6.8 Hz).

Example 232

4-N-cyclopropyl-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(quinolin-5-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 278; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.91 (1H, dd, J = 4 and 1.6 Hz), 8.66 (1H, d, J = 8.4 Hz), 8.14 (1H, d, J = 8.4 Hz), 7.89 – 7.85 (1H, m), 7.74 (1H, d, J = 6.8 Hz), 7.59 – 7.56 (1H, m), 6.26 (1H, s), 2.69 (1H, br s), 0.85 – 0.80 (2H, m), 0.62 – 0.59 (2H, m).

Example 233

(2E)-3-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoic acid.

Prepared according to general procedure 6 from (2E)-3-[4-(dihydroxyboranyl)phenyl]prop-2-enoic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 271.

Example 234

tert-butyl 3-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-azetidine-1-carboxylate.

Prepared according to general procedure 3 from tert-butyl 3-(aminomethyl)azetidine-1-carboxylate and 4-chloro-6-(2,3-dimethylphenyl)-pyrimidin-2-amine. LCMS $[M+H]^+$ 384; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 7.6 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.07 (1H, d, J = 7.6 Hz), 5.82 (s, 1H), 4.05 – 4.00 (2H, m), 3.73 – 3.69 (2H, m), 3.60 – 3.59 (2H, m), 2.92 – 2.82 (1H, m), 2.33 (3H, s), 2.21 (3H, s), 1.45 (9H, s).

Example 235

4-*N*-cyclopropyl-6-(1H-indol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (1H-indol-5-yl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 266.

Example 236

1-(3-{[2-amino-6-(1H-indol-5-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

Prepared according to general procedure 2 from (1H-indol-5-yl)boronic acid and 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one. LCMS $[M+H]^+$ 351; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.02 (1H, d, J = 1.6 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.48 (1H, dd, J = 8.4 and 2.0 Hz), 7.42 (1H, d, J = 3.2 Hz), 6.64 (1H, d, J = 3.2 Hz), 6.37 (1H, s), 3.57 – 3.51 (4H, m), 3.42 (2H, t, J = 7.2 Hz), 2.43 (2H, t, J = 8.0 Hz), 2.10 (2H, quintet, J = 8.4 Hz), 1.93 (2H, quintet, J = 7.2 Hz).

Example 237

tert-Butyl 4-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate.

Prepared according to general procedure 3 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and tert-butyl 4-aminopiperidine-1-carboxylate. LCMS $[M+H]^+$ 398; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 6.8 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.2 and 0.8 Hz), 5.82 (1H, s), 4.07 – 4.05 (2H, m), 2.99 (2H, m), 2.33 (3H, s), 2.22 (3H, s), 2.03 – 1.99 (2H, s), 1.49 (9H, s), 1.42 – 1.39 (2H, m).

Example 238

Ethyl 4-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate.

Prepared according to general procedure 3 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and ethyl 4-aminopiperidine-1-carboxylate. LCMS $[M+H]^+$ 370; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.19 (1H, d, J = 7.2 Hz), 7.11 (1H, t, J = 7.2 Hz), 7.08 (1H, d, J = 7.6 Hz), 5.82 (1H, s), 4.15 (2H, q, J = 7.2 Hz), 4.15 – 4.09 (3H, m), 3.07 – 2.98 (2H, m), 2.33 (3H, s), 2.21 (3H, s), 2.04 – 2.01 (2H, m), 1.48 – 1.39 (2H, m), 1.29 (4H, t, J = 7.2 Hz).

Example 239

tert-Butyl (3-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)-2,2-dimethyl-propyl)carbamate.

Prepared according to general procedure 3 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and tert-butyl N-(3-amino-2,2-dimethylpropyl)carbamate. LCMS $[M+H]^+$ 400.

Example 240

6-(5-chloro-4-methoxy-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-4-methoxy-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 279.

Example 241

6-(3-chloro-2-methylphenyl)-4-N-[(1R)-1-phenylethyl]pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and (+)1-phenylethan-1-amine (0,050 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 339; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (1 H, d, J=8.08 Hz) 7.62 - 7.71 (1 H, m) 7.24 - 7.47 (7 H, m) 6.23 (0.1 H, s) 6.09 (0.9 H, s) 5.35 (1 H, quin, J=7.26 Hz) 2.31 (2.7 H, s) 2.13 (0.3 H, s) 1.46 - 1.57 (3 H, m).

Example 242

6-(3-chloro-2-methylphenyl)-4-N-(2-phenylpropan-2-yl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and 2-phenylpropan-2-amine (0,050 mL) were stirred neat at 150°C for 24 hours. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC

to give the desired product. LCMS $[M+H]^+$ 353; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.45 (1 H, br. s.) 8.96 (1 H, br. s.) 7.12 - 7.79 (8 H, m) 6.22 (1 H, s) 2.31 (3 H, s) 1.79 (6 H, br. s.)

Example 243

6-(3-chloro-2-methylphenyl)-4-N-[1-(1H-indol-3-yl)propan-2-yl]pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and 1-(1H-indol-3-yl)propan-2-amine (0,050 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 392; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.34 (1 H, br. s.) 10.90 (0.9 H, s) 10.85 (0.1 H, br. s.) 8.79 (0.9 H, d, J=7.83 Hz) 8.63 (0.1 H, d, J=9.09 Hz) 7.66 (0.9 H, dd, J=7.20, 2.15 Hz) 7.62 (0.1 H, d, J=7.58 Hz) 7.54 (1 H, d, J=7.83 Hz) 7.28 - 7.43 (3 H, m) 7.20 (0.9 H, d, J=2.27 Hz) 6.95 - 7.13 (2 H, m) 6.89 - 6.95 (0.1 H, m) 5.99 (0.9 H, s) 5.93 (0.1 H, s) 4.39 - 4.50 (1 H, m) 2.86 - 3.03 (2 H, m) 2.30 (2.7 H, s) 2.14 (0.3 H, s) 1.27 (0.3 H, d, J=6.32 Hz) 1.20 (2.7 H, d, J=6.57 Hz).

Example 244

4-N-{bicyclo[2.2.1]heptan-2-yl}-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and bicyclo[2.2.1]heptan-2-amine (0,050 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (~2 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 329; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.66 (1 H, br. s.) 7.62 - 7.69 (1 H, m) 7.35 - 7.44 (2 H, m) 5.99 (1 H, s) 3.87 (1 H, br. s.) 2.30 (3 H, s) 2.27 -2.35 (1 H, m) 2.24 (1 H, d, J=3.28 Hz) 1.70 - 1.80 (1 H, m) 1.33 - 1.60 (4 H, m) 1.09 - 1.26 (3 H, m)

Example 245

6-(3-chloro-2-methylphenyl)-4-N-ethylpyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol), 70% ethanamine (0,050 mL) and n-butanol (2 mL) were stirred in a sealed tube at 120°C for 8 hours. The solvent was removed in vacuo and the crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC

to give the desired product. LCMS $[M+H]^+$ 263; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.49 (1 H, br. s.) 8.86 (0.9 H, t, J=5.18 Hz) 8.63 - 8.73 (0.1 H, m) 7.60 - 7.70 (1 H, m) 7.34 - 7.45 (2 H, m) 6.34 (0.1 H, br. s.) 6.02 (0.9 H, s) 3.23 - 3.58 (2 H, m) 2.33 (0.3 H, s) 2.30 (2.7 H, s) 1.18 (2.7 H, t, J=7.20 Hz) 1.08 - 1.14 (0.3 H, m)

Example 246

6-(3-chloro-2-methylphenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol), propan-2-amine (0,050 mL) and n-butanol (2 mL) were stirred in a sealed tube at 120°C for 8 hours. The solvent was removed in vacuo and the crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 277.

Example 247

4-N-[2-(2-chlorophenoxy)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (13 mg, 0,054 mmol) and 1-(2-aminoethoxy)-2-chlorobenzene (18 mg, 0,11 mmol) were stirred neat at 150°C for 1 h. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 369.

Example 248

4-N-[2-(5-chloro-1H-1,3-benzodiazol-2-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (23 mg, 0,10 mmol), 2-(5-chloro-1H-1,3-benzodiazol-2-yl)ethan-1-amine (20 mg, 0,10 mmol), Et_3N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 393.

Example 249

4-N-[2-(2,5-dimethyl-1H-indol-3-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol) and 2-(2,5-dimethyl-1H-indol-3-yl)ethan-1-amine (0,020 mL) were stirred neat at 150°C

for 1 hour. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 386; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.30 (1 H, br. s.) 10.65 (0.9 H, s) 10.60 (0.1 H, s) 8.82 (0.9 H, t, J=5.56 Hz) 8.56 - 8.67 (0.1 H, m) 7.06 - 7.41 (5 H, m) 6.70 - 6.85 (1 H, m) 5.97 (0.9 H, s) 5.76 (0.1 H, s) 3.58 (1.8 H, q, J=6.65 Hz) 3.48 (0.2 H, d, J=6.32 Hz) 2.93 (0.8 H, t, J=7.07 Hz) 2.80 - 2.89 (0.2 H, m) 2.23 - 2.38 (9 H, m) 2.17 (2.7 H, s) 2.06 (0.3 H, s)

Example 250
6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-3-yloxy)propyl]pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol) and 3-[(1-aminopropan-2-yl)oxy]pyridine (15 mg, 0,10 mmol) were stirred neat at 150°C for 1 h. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 350.

Example 251
6-(2,3-dimethylphenyl)-4-N-(1H-indazol-5-ylmethyl)pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), 1H-indazol-5-ylmethanamine (15 mg, 0,10 mmol), Et_3N (0.040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 345.

Example 252
6-(2,3-dimethylphenyl)-4-N-(1H-indazol-6-ylmethyl)pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), 1H-indazol-6-ylmethanamine (15 mg, 0,10 mmol), Et3N (0.040 mL), 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 h. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 345

Example 253
6-(2,3-dimethylphenyl)-4-N-[(2-methoxypyridin-4-yl)methyl]pyrimidine-2,4-diamine.

4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), (2-methoxypyridin-4-yl)methanamine (14 mg, 0,10 mmol), Et_3N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 336.

Example 254

4-N-[(5-chloropyrazin-2-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), (5-chloropyrazin-2-yl)methanamine (14 mg, 0,10 mmol), Et_3N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 341.

Example 255

6-(2,3-dimethylphenyl)-4-N-{imidazo[1,2-a]pyridin-2-ylmethyl}pyrimidine-2,4-diamine.

4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), imidazo[1,2-a]pyridin-2-ylmethanamine (14 mg, 0,10 mmol), Et_3N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 345.

Example 256

tert-butyl 4-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-(methoxymethyl)phenoxymethyl}piperidine-1-carboxylate.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), tert-butyl 4-[4-(dimethoxyboranyl)-2-(methoxymethyl)phenoxymethyl]piperidine-1-carboxylate (67 mg, 0.17 mmol), potassium carbonate (41 mg, 0.30 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (5 mL) and water (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 458.

Example 257

6-[3-(methoxymethyl)-4-(piperidin-4-ylmethoxy)phenyl]-4-N-methylpyrimidine-2,4-diamine hydrochloride.

A solution of tert-butyl 4-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-(methoxymethyl)-phenoxymethyl}piperidine-1-carboxylate (45 mg, 0.10 mmol; Example 256) in methanol (3 mL) was treated with 4M HCl in 1,4-dioxane (1 mL). The mixture was stirred at r.t. for 3 h, concentrated and dried in vacuo to give the desired product. LCMS $[M+H]^+$ 358.

Example 258

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-methylbenzonitrile.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (3-cyano-2-methylphenyl)boronic acid (29 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 240.

Example 259

6-(4-methoxy-2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (4-methoxy-2,3-dimethylphenyl)boronic acid (32 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 259.

Example 260

6-(4-fluoro-2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (4-fluoro-2,3-dimethylphenyl)boronic acid (30 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 247.

Example 261

6-(2,3-dihydro-1-benzofuran-7-yl)-4-N-methylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (2,3-dihydro-1-benzofuran-7-yl)boronic acid (30 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 243.

Example 262

4-N-methyl-6-[2-methyl-5-(morpholine-4-sulfonyl)phenyl]pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), [2-methyl-5-(morpholine-4-sulfonyl)phenyl]boronic acid (51 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)-palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 364.

Example 263

4-N-[2-(4-chlorophenyl)ethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (28 mg, 0.10 mmol), 2-(4-chlorophenyl)ethan-1-amine (22 mg, 0.14 mmol) and Hünig's base (36 µL, 0.20 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 393. 1H NMR (400 MHz, DMSO-d6) δ ppm 12.56 (br. s., 1 H), 8.90 (br. s., 1 H), 7.83 - 7.89 (m, 1 H), 7.51 - 7.59 (m, 2 H), 7.35 - 7.41 (m, 2 H), 7.28 - 7.34 (m, 2 H), 6.11 (s, 1 H), 3.63 (q, J=6.4 Hz, 2 H), 2.89 (t, J=7.1 Hz, 2 H).

Example 264

4-N-[2-(4-chlorophenyl)ethyl]-6-(2-methylphenyl)pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), (2-methylphenyl)boronic acid (20 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)-palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in

a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 339.

Example 265

4-N-[2-(4-chlorophenyl)ethyl]-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), [3-(trifluoromethyl)phenyl]boronic acid (27 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 393.

Example 266

4-N-[2-(4-chlorophenyl)ethyl]-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), (quinolin-5-yl)boronic acid (25 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 376.

Example 267

4-N-[2-(4-chlorophenyl)cyclopropyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 2-(4-chlorophenyl)cyclopropan-1-amine (43 mg, 0.26 mmol) and Hünig's base (90 µL, 0.52 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 365.

Example 268

6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 2-(pyridin-3-yl)ethan-1-amine (21 mg, 0.17 mmol) and Hünig's base (42

µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 320.

Example 269

3-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)phenol.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(2-aminoethyl)phenol (23 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 335.

Example 270

6-(2,3-dimethylphenyl)-4-N-[3-(morpholin-4-yl)propyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(morpholin-4-yl)propan-1-amine (24 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 342.

Example 271

tert-butyl N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-carbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(2-aminoethyl)carbamate (27 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 358.

Example 272

N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)acetamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), N-(2-aminoethyl)acetamide (17 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight.

The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 300.

Example 273

benzyl N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-carbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), benzyl N-(2-aminoethyl)carbamate hydrochloride (39 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 392.

Example 274

tert-butyl N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-N-methylcarbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(2-aminoethyl)-N-methylcarbamate (29 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 372.

Example 275

tert-butyl N-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-carbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(3-aminopropyl)carbamate (29 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 372.

Example 276

6-(2,3-dimethylphenyl)-4-N-[3-(5-methyl-1H-pyrazol-3-yl)propyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(5-methyl-1H-pyrazol-4-yl)propan-1-amine (23 mg, 0.17 mmol) and

Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 337.

Example 277

3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-1-(morpholin-4-yl)propan-1-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), 3-amino-1-(morpholin-4-yl)propan-1-one (22 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC.

LCMS $[M+H]^+$ 356.

Example 278

4-N-[(4-benzylmorpholin-2-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (4-benzylmorpholin-2-yl)methanamine (29 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC.

LCMS $[M+H]^+$ 404.

Example 279

6-(2,3-dimethylphenyl)-4-N-[(4-methanesulfonylphenyl)methyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (4-methanesulfonylphenyl)methanamine hydrochloride (31 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 383.

Example 280

6-(2,3-dimethylphenyl)-4-N-{[4-(4-methylpiperazin-1-yl)phenyl]methyl}pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), [4-(4-methylpiperazin-1-yl)phenyl]methanamine (29 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 403.

Example 281

4-N-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (S)-quinuclidin-3-amine hydrochloride (29 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 324.

Example 282

tert-butyl 2-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-pyrrolidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (28 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 398.

Example 283

tert-butyl 4-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-piperidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (30 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 412.

Example 284

1-(3-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (19 mg, 0.070 mmol) and 1-(3-aminopropyl)pyrrolidin-2-one (49 µL, 0.35 mmol) in n-butanol (1 mL) was heated in a sealed tube at 110°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 380.

Example 285

1-(3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (19 mg, 0.076 mmol) and 1-(3-aminopropyl)pyrrolidin-2-one (53 µL, 0.38 mmol) in n-butanol (1 mL) was heated in a sealed tube at 110°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 360.

Example 286

1-(3-{[2-amino-6-(4-fluoro-2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (4-fluoro-2,3-dimethylphenyl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 358.

Example 287

1-(3-{[2-amino-6-(4-methoxy-2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (4-methoxy-2,3-dimethylphenyl)boronic acid (20 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 370.

Example 288

1-(3-{[2-amino-6-(4-methyl-1H-indazol-5-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (4-methyl-1H-indazol-5-yl)boronic acid (19 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 366.

Example 289

1-[3-({2-amino-6-[2-methyl-5-(morpholine-4-sulfonyl)phenyl]pyrimidin-4-yl}amino)propyl]pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), [2-methyl-5-(morpholine-4-sulfonyl)phenyl]boronic acid (31 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 475.

Example 290

1-(3-{[2-amino-6-(2,3-dihydro-1-benzofuran-7-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (2,3-dihydro-1-benzofuran-7-yl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 354.

Example 291

1-(3-{[2-amino-6-(2,5-dimethylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (2,5-dimethylphenyl)boronic acid (17 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium

tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 340.

Example 292

1-(3-{[2-amino-6-(5-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (5-chloro-2-methylphenyl)boronic acid (19 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 360.

Example 293

1-[3-({2-amino-6-[2-(trifluoromethyl)phenyl]pyrimidin-4-yl}amino)propyl]pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), [2-(trifluoromethyl)phenyl]boronic acid (21 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 380.

Example 294

1-(3-{[2-amino-6-(1H-indol-4-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (1H-indol-4-yl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)-palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 351.

Example 295

4-N-{[1-(4-chlorophenyl)cyclopropyl]methyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (47 mg, 0.20 mmol), [1-(4-chlorophenyl)cyclopropyl]methanamine hydrochloride (65 mg, 0.30 mmol) and Hünig's base (70 µL, 0.40 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 130°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 379.

Example 296

4-(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (41 mg, 0.15 mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (45 mg, 0.23 mmol) and Hünig's base (39 µL, 0.23 mmol) in n-butanol (2 mL) was heated in a sealed tube at 90°C for 48 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 438.

Example 297

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (38 mg, 0.15 mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (45 mg, 0.23 mmol) and Hünig's base (39 µL, 0.23 mmol) in n-butanol (2 mL) was heated in a sealed tube at 90°C for 48 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 418. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.85 (d, J=8.5 Hz, 2H), 7.46 (d, J= 8.5 Hz, 2H), 7.43 (dd, J= 7.58, 1.74 Hz, 1H), 7.25-7.18 (m, 2H), 5.80 (1H, s), 3.66 (m, 2H), 3.02 (t, J=7.3 Hz, 2H), 2.33 (s, 3H).

Example 298

4-N-(Adamantan-1-yl)-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

A mixture of the 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and adamantylamine (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS $[M+H]^+$ 389.

Example 299

6-(2,3-dichlorophenyl)-4-N-[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (50 mg) was heated at 150°C for 1h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS $[M+H]^+$ 391.

Example 300

6-(2,3-Dichlorophenyl)-4-N-({3-[(4-methylpiperidin-1-yl)methyl]phenyl}methyl)-pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and {3-[(4-methylpiperidin-1-yl)methyl]phenyl}methanamine (50 mg) was heated at 150°C for 1h. The mixture was cooled, diluted in methanol and then purified by preparative HPLC. LCMS $[M+H]^+$ 456.

Example 301

4-(2-{[2-Amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)phenol.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and 4-(2-aminoethyl)phenol (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS $[M+H]^+$ 375.

Example 302

Ethyl 4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}piperidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and ethyl 4-aminopiperidine-1-carboxylate (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS $[M+H]^+$ 410.

Example 303

N-(4-{[2-Amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)acetamide.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with N-(4-aminobutyl)acetamide (1 equiv.) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 368.

Example 304

6-(2,3-Dichlorophenyl)-4-N-{tricyclo[3.3.1.0^{3,7}]nonan-3-yl}pyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with tricyclo[3.3.1.0^{3,7}]nonan-3-amine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 375.

Example 305

6-(2,3-Dichlorophenyl)-4-N-{[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl}pyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with [4-(1,2,3-thiadiazol-4-yl)phenyl]methanamine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 429.

Example 306

4-N-[2-(1-Benzylpiperidin-4-yl)ethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with 2-(1-benzylpiperidin-4-yl)ethan-1-amine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 456.

Example 307

6-[2-[[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]ethylamino]-3,3-dimethyl-4H-1,4-benzoxazin-2-one

Step 1. 6-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-3,3-dimethyl-4H-1,4-benzoxazin-2-one.

Step 2. The title compound was prepared according to general procedure 9 from intermediate 21 and 6-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one $[M+H]^+$ 473. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.76 - 7.82 (m, 1 H), 7.48 - 7.51 (m, 2 H), 6.80 (d, *J*=8.5 Hz, 1 H), 6.48 (dd, *J*=8.7, 2.7 Hz, 1 H), 6.40 (d, *J*=2.5 Hz, 1 H), 6.13 (s, 1 H), 3.76 (t, *J*=6.0 Hz, 3 H), 3.44 (t, *J*=6.0 Hz, 3 H), 1.42 (s, 6 H).

Example 308

N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}-3-hydroxypyridine-2-carboxamide.

Equimolar quantities of 3-hydroxypyridine-2-carboxylic acid (0.24 mmol) and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine were dissolved in 2 ml DMF followed by addition of hydroxybenzotriazole (1.0 eq) and N,N'-dicyclohexylcarbodiimide (1.5 eq). The solution was stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC.

LCMS $[M+H]^+$ 337; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.15 (1 H, br. s.), 11.17 (1 H, s), 8.86 (1 H, m, J=5.05 Hz), 8.25 - 8.35 (2 H, m), 8.03 (1 H, dd, J=8.08, 1.26 Hz), 7.59 - 7.68 (2 H, m), 7.52 (2 H, dd, J=8.46, 1.39 Hz), 6.36 (1 H, s), 2.95 (3 H, d, J=4.80 Hz).

Example 309

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enamide.

To a stirred suspension of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.29 mmol) and triethylamine (1.5 equiv.) in acetonitrile (2 mL) at 0 °C was slowly added prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 270; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.35 (1 H, s), 8.23 (1 H, t, J=1.89 Hz), 7.79 (1 H, d, J=8.08 Hz), 7.56 - 7.69 (4 H, m), 7.34 - 7.52 (4 H, m), 6.88 (1 H, s), 6.84 (1 H, s), 6.18 (1 H, s), 5.98 (2 H, s), 2.80 (3 H, d, J=4.80 Hz).

Example 310

(2E)-N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-3-phenylprop-2-enamide.

To a suspension of the 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.25 mmol) and triethylamine (1.5 equiv.) in acetonitrile (2 mL) at 0 °C was added drop wise, with stirring, the (E)-3-phenylprop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 346; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.35 (s, 1 H), 8.23 (t, J=1.89 Hz, 1 H), 7.79 (d, J=8.08

Hz, 1 H), 7.56 - 7.69 (m, 4 H), 7.34 - 7.52 (m, 4 H), 6.88 (s, 1 H), 6.84 (s, 1 H), 6.18 (s, 1 H), 5.98 (s, 2 H), 2.80 (d, J=4.80 Hz, 3 H).

Example 311

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]-2-methylphenyl}prop-2-enamide.

To a suspension of 6-(3-amino-2-methyl-phenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.39 mmol) and triethylamine (1.5 equiv.) in acetonitrile (3 ml) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 284; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.57 (1 H, s), 7.41 (1 H, d, J=7.58 Hz), 7.20 (1 H, t, J=7.83 Hz), 7.10 (1 H, d, J=6.82 Hz), 6.83 (1 H, br. s.), 6.54 (1 H, dd, J=17.05, 10.23 Hz), 6.25 (1 H, dd, J=17.05, 2.15 Hz), 5.97 (2 H, s), 5.73 - 5.78 (1 H, m), 5.71 (1 H, s), 2.77 (3 H, d, J=4.55 Hz), 2.14 (3 H, s).

Example 312

(2E)-N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-4-(dimethylamino)but-2-enamide.

To a solution of 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine (0.29 mol) in acetonitrile (4 mL) was added successively (E)-4-(dimethylamino)but-2-enoic acid; hydrochloride (1.0 equiv.), triethylamine (3.0 equiv.) and n-propanephosphonic acid anhydride (T3P, 2.0 equiv.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 327; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.17 (1 H, s), 8.20 (1 H, t, J=1.77 Hz), 7.71 (1 H, d, J=8.08 Hz), 7.58 (1 H, d, J=7.83 Hz), 7.36 (1 H, t, J=7.83 Hz), 6.81 - 6.96 (1 H, m), 6.70 - 6.80 (1 H, m), 6.28 (1 H, dt, J=15.35, 1.55 Hz), 6.16 (1 H, s), 5.97 (2 H, s), 3.06 (2 H, dd, J=6.06, 1.52 Hz), 2.79 (3 H, d, J=4.80 Hz), 2.18 (6 H, s).

Example 313

N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}ethene-1-sulfonamide.

To a suspension of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.20 mmol) and triethylamine (1.1 equiv.) in acetonitrile (1.5 mL) at -60 °C was added drop wise, with stirring, ethenesulfonyl chloride (0.9 equiv.) in 0.5 ml acetonitrile. The mixture was allowed to warm to rt, and stirred for 2 h. The solution was then

filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 306; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.98 (1 H, br. s.), 10.38 (1 H, br. s.), 8.79 (1 H, br. s.), 7.31 - 7.60 (4 H, m), 6.85 (1 H, dd, J=16.42, 9.85 Hz), 6.25 (1 H, s), 6.18 (1 H, d, J=16.42 Hz), 6.08 (1 H, d, J=9.85 Hz), 2.93 (3 H, d, J=4.80 Hz).

Example 314

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-ynamide.

To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.30 mol) in acetonitrile (5 mL) at 0 °C was added successively prop-2-ynoic acid (1.0 equiv.), triethylamine (2.0 equiv.) and n-propanephosphonic acid anhydride (T3P, 1.7 equiv.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 268; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.19 (1 H, br. s.), 7.84 (1 H, d, J=7.83 Hz), 7.65 (1 H, d, J=7.83 Hz), 7.46 (1 H, d, J=13.39 Hz), 7.38 (1 H, t, J=7.83 Hz), 7.00 (1 H, d, J=13.89 Hz), 6.28 (1 H, br. s.), 5.97 (2 H, s), 2.78 (3 H, d, J=4.55 Hz).

Example 315

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-oxopropanamide.

To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.39 mol) in acetonitrile (4 mL) was added successively pyruvic acid (1.0 equiv.), triethylamine (2.5 equiv.) and n-propanephosphonic acid anhydride (T3P, 2.0 equiv.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 286.

Example 316

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-oxo-2-phenylacetamide.

To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.42 mol) in acetonitrile (4 mL) was added successively 2-oxo-2-phenyl-acetic acid (0.9 equiv.), triethylamine (2.5 equiv.) and n-propanephosphonic acid anhydride (T3P, 2.0 equiv.). The resulting mixture was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 348; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.30 - 8.36 (1 H, m), 8.00 - 8.11 (2 H, m), 7.66 - 7.84 (3 H, m), 7.59 - 7.66 (2 H, m), 7.45 (1 H, t, J=7.96 Hz), 6.90 (1 H, br. s.), 6.19 (1 H, s), 6.01 (2 H, s), 2.80 (3 H, d, J=4.80 Hz).

Example 317

N-{4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enamide.

To a suspension of 6-(4-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.29 mmol) and triethylamine (1.5 equiv.) in tetrahydrofuran (2 ml) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 270; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.28 (1 H, s), 7.89 (2 H, d, J=8.8 Hz), 7.58 - 7.75 (2 H, m), 6.76 (1 H, br. s.), 6.40 - 6.49 (1 H, m), 6.24 - 6.30 (1 H, m), 6.17 (1 H, s), 5.94 (2 H, s), 5.58 - 5.80 (1 H, m), 2.79 (3 H, d, J=4.8 Hz).

Example 318

N-({4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}methyl)prop-2-enamide.

To a suspension of 6-[4-(aminomethyl)phenyl]-4-N-methyl-pyrimidine-2,4-diamine (0.29 mmol) and triethylamine (1.5 equiv.) in tetrahydrofuran (2 ml) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 284.

Example 319

N-({3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}methyl)prop-2-enamide.

To a suspension of 6-[3-(aminomethyl)phenyl]-4-N-methyl-pyrimidine-2,4-diamine (0.16 mmol) and triethylamine (1.5 equiv.) acetonitrile (4 mL) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to room temperature, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 284.

Example 320

N-{3-[2-Amino-6-(ethylamino)pyrimidin-4-yl]-4-methylphenyl}prop-2-enamide.

To a suspension of 6-(5-amino-2-methyl-phenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.48 mmol) and triethylamine (1.7 equiv.) in acetonitrile (3 mL) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 equiv.). The mixture was allowed to warm to rt and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 284; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.10 (1 H, s), 7.46 - 7.75 (2 H, m), 7.16 (1 H, d, J=8.34 Hz), 6.80 (1 H, br.

s.), 6.37 - 6.46 (1 H, m), 6.23 (1 H, dd, J=17.05, 2.15 Hz), 5.95 (2 H, s), 5.62 - 5.84 (2 H, m), 2.77 (3 H, d, J=4.55 Hz), 2.27 (3 H, s).

Example 321

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-5-chloro-2-hydroxybenzamide.

Equimolar quantities of 5-chloro-2-hydroxy-benzoic acid and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL) followed by adding hydroxybenzotriazole (1.0 eq) and N,N'-dicyclohexyl-carbodiimide (1.5 eq). The solution was stirred under rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 370; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 15.10 (1 H, br. s), 8.08 - 8.16 (1 H, m), 7.86 (1 H, d, J=7.58 Hz), 7.64 (1 H, d, J=3.03 Hz), 7.49 (1 H, d, J=7.33 Hz), 7.32 (1 H, t, J=7.96 Hz), 6.93 (1 H, dd, J=8.84, 3.03 Hz), 6.78 - 6.89 (1 H, m), 6.40 (1 H, d, J=8.84 Hz), 6.20 (1 H, s), 6.03 (2 H, s), 2.80 (3 H, d, J=4.55 Hz).

Example 322

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxyacetamide.

Equimolar quantities of 2-hydroxyacetic acid and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in 2 ml DMF followed by adding hydroxybenzotriazole (1.0 eq) in 1 mL DMF and N,N'-dicyclohexylcarbo-diimide (1.5 eq, dissolved in xylene). The solution was stirred under room temperature overnight. The mixture was then filtrated and purified by preparative. LCMS $[M+H]^+$ 274; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.06 (1 H, br. s.), 9.75 - 10.10 (1 H, m), 8.83 (1 H, d, J=4.55 Hz), 8.22 (1 H, s), 7.84 (1 H, d, J=9.35 Hz), 7.54 (1 H, t, J=7.96 Hz), 7.40 (1 H, d, J=8.08 Hz), 6.30 (1 H, s), 5.61 - 5.97 (1 H, m), 4.03 (2 H, s), 2.94 (3 H, d, J=4.80 Hz).

Example 323

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-(4-chlorophenyl)-2-hydroxyacetamide.

Equimolar quantities of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) and 2-(4-chlorophenyl)-2-hydroxy-acetic acid were dissolved in 2 ml DMF followed by adding hydroxybenzotriazole (1.0 eq) in 1 mL DMF and N,N'-dicyclohexylcarbodiimide (1.5 equiv.; as a solution in xylene). The solution was

stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 384; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.05 (1 H, s), 8.22 (1 H, t, J=1.89 Hz), 7.69 (1 H, d, J=8.59 Hz), 7.59 (1 H, d, J=6.57 Hz), 7.52 - 7.57 (2 H, m), 7.40 - 7.45 (2 H, m), 7.34 (1 H, t, J=7.96 Hz), 6.85 (1 H, br. s.), 6.14 (1 H, s), 6.04 (2 H, br. s.), 5.97 (1 H, s), 5.14 (1 H, s), 2.78 (3 H, d, J=4.80 Hz).

Example 324

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxy-2-phenylacetamide.

Equimolar quantities of 2-hydroxy-2-phenyl-acetic acid and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL) followed by adding hydroxybenzotriazole (1.0 eq) in DMF (1 mL) and N,N'-dicyclohexylcarbodiimide (1.5 eq, dissolved in xylene). The solution was stirred under rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 350; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.86 (1 H, br. s.), 10.25 (2 H, s), 8.25 (1 H, s), 7.85 (1 H, d, J=8.59 Hz), 7.48 - 7.63 (3 H, m), 7.26 - 7.46 (4 H, m), 6.56 (1 H, d, J=4.29 Hz), 6.28 (1 H, s), 5.15 (1 H, d, J=3.79 Hz), 2.93 (3 H, d, J=4.80 Hz).

Example 325

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-4-oxo-4-(pyrrolidin-1-yl)butanamide.

Equimolar quantities of 4-oxo-4-pyrrolidin-1-yl-butanoic acid and 6-(3-amino-phenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL) followed by adding hydroxybenzotriazole (1.0 eq) in DMF (1 mL) and N,N'-dicyclohexylcarbodiimide (1.5 eq, dissolved in xylene). The solution was stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 369.

Example 326

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxybenzamide.

Equimolar quantities of 2-hydroxybenzoic acid and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in MeCN (2 mL) followed by adding N,N'-dicyclohexylcarbodiimide (1.25 eq). The solution was

stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 336.

Example 327

1-{4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2,2,2-trifluoroethan-1-one. Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (0.25 mmol), [4-(trifluoroacetyl)phenyl]boronic ester (1.3 equiv.), sodium carbonate (3.2 equiv.), dioxane (2 mL) and water (0.5 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 hours. The mixture was then filtrated and purified by preparative HPLC. LCMS $[M+H]^+$ 297.

Example 328

6-[3-(Aminomethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine. Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (2.00 mmol), [3-(aminomethyl)phenyl]boronic acid (1.3 equiv.), sodium carbonate (3.2 equiv.), dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C overnight. The solvent were removed in vacuum and to the remaining solid was added ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate. The crude material was then purified by flash chromatography (0→15 % MeOH/DCM) to give the title compound. LCMS $[M+H]^+$ 230; ^{1}H NMR (400 MHz, DMSO-d_6 δ ppm 7.90 (1 H, s), 7.75 (1 H, d, J=6.32 Hz), 7.35 - 7.42 (3 H, m), 6.82 (1 H, br. S), 6.21 (1 H, s), 5.98 (2 H, s), 3.79 (2 H, s), 2.79 (3 H, d, J=4.80 Hz).

Example 329

6-[4-(Aminomethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine. Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.00 mmol), [4-(aminomethyl)phenyl]boronic acid (1.3 equiv.), sodium carbonate (4.2 equiv.), dioxane (4 ml) and water (1 ml) in a tube. The tube was sealed and the reaction was heated at 90°C overnight. The solvent were removed in vacuum and to the remaining solid was added ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate. The crude material was then purified

by flash chromatography (0→15 % MeOH/DCM) to give the title compound. LCMS $[M+H]^+$ 230; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.86 (2 H, d, J=7.58 Hz), 7.38 (2 H, d, J=8.59 Hz), 6.19 (1 H, s), 5.96 (2 H, s), 3.76 (2 H, s), 2.79 (3 H, d, J=4.80 Hz).

Example 330

4-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.12 mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 398; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.28 (1 H, br. s.), 8.87 (1 H, br. s.), 7.77 (2 H, d, J=8.34 Hz), 7.48 (2 H, d, J=8.34 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.32 (2 H, s), 7.23 - 7.28 (1 H, m), 7.18 - 7.23 (1 H, m), 5.99 (1 H, s), 3.67 (2 H, q, J=6.82 Hz), 2.98 (2 H, t, J=7.20 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

Example 331

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(4-methanesulfonylphenyl)ethan-1-amine (1.2 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 397.

Example 332

6-(2,3-Dimethylphenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethan-1-amine (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 324.

Example 333

4-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzonitrile.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethyl)benzonitrile (1.2 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 344; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.36 (1 H, br. s.), 8.87 (1 H, t, J=5.31 Hz), 7.80 (2 H, d, J=8.08 Hz), 7.51 (2 H, d, J=8.34 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.23 - 7.28 (1 H, m), 7.16 - 7.22 (1 H, m), 5.98 (1 H, s), 3.67 (2 H, q, J=6.65 Hz), 2.99 (2 H, t, J=7.20 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

Example 334

6-(2,3-Dimethylphenyl)-4-N-[2-(pyridin-4-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(pyridin-4-yl)ethan-1-amine (1.2 equiv.) and N,N-diisopropylethylamine (1.25 equiv.) in n-butanol (0.3 ml) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 320; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.45 (1 H, br. s.), 8.93 (1 H, t, J=5.56 Hz), 8.76 (2 H, d, J=6.32 Hz), 7.80 (2 H, d, J=6.32 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.25 (1 H, t, J=7.58 Hz), 7.17 - 7.21 (1 H, m), 5.99 (1 H, s), 3.68 - 3.83 (2 H, m), 3.13 (2 H, t, J=7.07 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

Example 335

4-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethoxy)benzonitrile.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethoxy)benzonitrile (1.2 equiv.) and N,N-diisopropylethylamine (1.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 360; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 12.37 (1 H, br. s.), 9.02 (1 H, t, J=5.31 Hz), 7.77 - 7.83 (2 H, m), 7.37 (1 H, d, J=7.33 Hz), 7.23 - 7.29 (1 H, m), 7.18 - 7.22 (1 H, m), 7.12 - 7.18 (2 H, m), 6.06 (1 H, s), 4.29 (2 H, t, J=5.43 Hz), 3.82 (2 H, q, J=5.22 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

Example 336

4-({[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.08 mmol), 4-(aminomethyl)benzene-1-sulfonamide (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 384; ^1H NMR (400 MHz, DMSO-d_6 δ ppm 7.74 - 7.81 (2 H, m), 7.49 - 7.54 (2 H, m), 7.46 (1 H, t, J=5.68 Hz), 7.30 (2 H, s), 7.12 - 7.21 (1 H, m), 7.01 - 7.12 (2 H, m), 6.00 (2 H, s), 5.76 (1 H, br. s.), 4.57 (2 H, br. s.), 2.26 (3 H, s), 2.15 (3 H, s).

Example 337

1-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-1,2-dihydropyridin-2-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.11 mmol), 1-(2-aminoethyl)-1,2-dihydropyridin-2-one (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 336.

Example 338

3-({[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-1,2-dihydropyridin-2-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.11 mmol), 3-(aminomethyl)-1,2-dihydropyridin-2-one (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 ml) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 322.

Example 339

6-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-5H,6H,7H-pyrrolo[3,4-b]pyridin-5-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.12 mmol), 6-(3-aminopropyl)-5H,6H,7H-pyrrolo[3,4-b]pyridin-5-one (0.9 equiv.) and triethylamine (1.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed

tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 389.

Example 340

6-({[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)pyridin-3-ol. A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.08 mmol), 6-(aminomethyl)pyridin-3-ol hydrochloride (0.9 equiv.) and triethylamine (2.5 equiv.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 322.

Example 341

4-N-[2-(3-Chlorophenyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 9 from 2-(3-chlorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 353; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.24 (s, 3 H) 2.31 (s, 3 H) 2.88 (t, J=7.07 Hz, 2 H) 3.56 (d, J=5.81 Hz, 2 H) 4.86 - 5.12 (m, 3 H) 5.79 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.17 (q, J=4.04 Hz, 1 H) 7.20 - 7.26 (m, 3 H).

Example 342

6-(2,3-Dimethylphenyl)-4-N-[3-(1H-imidazol-1-yl)propyl]pyrimidine-2,4-diamine. Prepared according to general procedure 9 from 3-(1H-imidazol-1-yl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ ppm 2.11 (t, J=6.82 Hz, 2 H) 2.20 (s, 3 H) 2.32 (s, 3 H) 3.38 (br. s., 2 H) 4.13 (t, J=6.95 Hz, 2 H) 5.82 (s, 1 H) 6.98 (br. s., 1 H) 7.05 - 7.23 (m, 4 H) 7.69 (br. s., 1 H).

Example 343

4-N-[2-(4-Chlorophenyl)propyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. Prepared according to general procedure 9 from 2-(4-chlorophenyl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 367; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.31 (d, J=7.07 Hz, 3 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 2.97 - 3.09 (m, 1 H) 3.28 - 3.40 (m, 1 H) 3.46 - 3.66 (m, 1 H) 4.74 (br. s., 1 H) 4.95 (br. s., 2 H) 5.74 (s, 1 H) 7.09 - 7.14 (m, 2 H) 7.14 - 7.19 (m, 3 H) 7.28 - 7.33 (m, 2 H).

Example 344

6-(2,3-Dimethylphenyl)-4-N-[2-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-fluorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.23 (s, 3 H) 2.29 - 2.34 (m, 3 H) 2.89 - 2.96 (m, 3 H) 3.49 - 3.60 (m, 1 H) 3.76 (d, J=6.06 Hz, 3 H) 5.77 (s, 4 H) 7.00 - 7.07 (m, 3 H) 7.08 - 7.12 (m, 2 H) 7.13 - 7.22 (m, 5 H) 7.28 - 7.32 (m, 1 H).

Example 345

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 418; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.74 - 1.81 (m, 4 H) 2.22 (s, 3 H) 2.30 (s, 3 H) 2.46 - 2.69 (m, 5 H) 3.49 (br. s., 2 H) 3.81 (s, 3 H) 4.88 (br. s., 2 H) 5.04 - 5.18 (m, 1 H) 5.74 (s, 1 H) 6.85 - 6.90 (m, 2 H) 7.09 - 7.12 (m, 2 H) 7.13 - 7.17 (m, 1 H) 7.24 - 7.29 (m, 2 H).

Example 346

4-N-{[4-(Dimethylamino)phenyl]methyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-(aminomethyl)-N,N-dimethylaniline and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 348.

Example 347

4-N-[2-(Benzenesulfonyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(benzenesulfonyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 383; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.22 (s, 3 H) 2.31 (s, 3 H) 3.41 - 3.46 (m, 2 H) 3.86 (q, J=6.06 Hz, 2 H) 5.10 (br. s., 2 H) 5.41 - 5.53 (m, 1 H) 5.76 (s, 1 H) 7.07 - 7.16 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.57 - 7.63 (m, 2 H) 7.66 - 7.71 (m, 1 H) 7.92 - 7.97 (m, 2 H),

Example 348

6-(2,3-Dimethylphenyl)-4-N-{[1-(4-fluorophenyl)-1H-pyrazol-4-yl]methyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from [1-(4-fluorophenyl)-1H-pyrazol-4-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 389; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.22 (s, 3 H) 2.29 (s, 3 H) 4.47 (d, J=5.31 Hz, 2 H) 5.11 - 5.41 (m, 3 H) 5.85 (s, 1 H) 7.10 - 7.19 (m, 5 H) 7.59 - 7.65 (m, 2 H) 7.68 (s, 1 H) 7.85 (s, 1 H)

Example 349

6-(2,3-dimethylphenyl)-4-N-{2-[5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-[5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl]ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 387.

Example 350

6-(2,3-Dimethylphenyl)-4-N-{[1-(pyrimidin-2-yl)piperidin-3-yl]methyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from [1-(pyrimidin-2-yl)piperidin-3-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 390; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.41 (m, 1 H) 1.48 - 1.60 (m, 1 H) 1.75 (m, 1 H) 1.85 - 1.98 (m, 2 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 3.13 - 3.48 (m, 4 H) 4.15 - 4.24 (m, 1 H) 4.30 (m, 1 H) 5.11 (br. s., 2 H) 5.39 (br. s., 1 H) 5.82 (s, 1 H) 6.45 (t, J=4.80 Hz, 1 H) 7.10 - 7.19 (m, 3 H) 8.28 - 8.31 (d, J=4.80 Hz, 2 H).

Example 351

6-(2,3-Dimethylphenyl)-4-N-[2-(6-methoxy-1H-1,3-benzodiazol-2-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(6-methoxy-1H-1,3-benzodiazol-2-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 389; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 (d, J=8.59 Hz, 1 H) 7.12 (d, J=6.82 Hz, 1 H) 7.05 (t, J=7.58 Hz, 1 H) 7.01 (d, J=8.08 Hz, 2 H) 6.85 (dd, J=8.72, 2.40 Hz, 1 H) 5.88 (br. s., 1 H) 5.79 (s, 1 H) 5.11 - 5.43 (m, 2 H)

3.82 - 3.90 (m, 2 H) 3.81 (s, 3 H) 3.12 (t, J=6.19 Hz, 2 H) 2.24 (s, 3 H) 2.16 (s, 3 H)

Example 352

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-methyl-1,3-thiazol-5-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.23 (s, 3 H) 2.30 (s, 3 H) 2.40 (s, 3 H) 3.07 (t, J=6.82 Hz, 2 H) 3.56 (q, J=6.48 Hz, 2 H) 5.01 (br. s., 3 H) 5.79 (s, 1 H) 7.11 - 7.14 (m, 2 H) 7.17 (q, J=4.55 Hz, 1 H) 8.59 (s, 1 H).

Example 353

4-N-[(3-Cyclopropyl-1H-pyrazol-5-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (3-cyclopropyl-1H-pyrazol-5-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 335; ^1H NMR (400 MHz, CD_3OD) δ ppm 0.63 - 0.71 (m, 2 H) 0.93 (br. d, J=7.33 Hz, 2 H) 1.83 - 1.93 (m, 1 H) 2.18 (s, 3 H) 2.31 (s, 3 H) 4.50 (br. s., 2 H) 5.86 (s, 1 H) 5.92 (s, 1 H) 7.03 - 7.22 (m, 3 H).

Example 354

4-N-[3-(3,5-Dimethyl-1H-pyrazol-1-yl)propyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 3-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 351; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.05 (quin, J=6.44 Hz, 2 H) 2.20 (s, 3 H) 2.21 (d, J=0.51 Hz, 3 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 3.28 - 3.38 (m, 2 H) 4.07 (t, J=6.57 Hz, 2 H) 5.00 (br. s., 2 H) 5.36 (br. s., 1 H) 5.74 (s, 1 H) 5.78 (s, 1 H) 7.10 - 7.14 (m, 2 H) 7.16 (q, J=4.29 Hz, 1 H).

Example 355

6-(2,3-Dimethylphenyl)-4-N-{[1-(pyridin-2-yl)piperidin-3-yl]methyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from [1-(pyridin-2-yl)piperidin-3-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS

$[M+H]^+$ 389; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 - 1.40 (m, 1 H) 1.53 - 1.67 (m, 1 H) 1.73 - 1.83 (m, 1 H) 1.88 - 2.00 (m, 2 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 3.00 (br. t, J=11.40 Hz, 1H) 3.09 (ddd, J=12.95, 10.04, 3.28 Hz, 1 H) 3.17 - 3.40 (m, 2 H) 3.91 (dt, J=12.88, 4.29 Hz, 1 H) 4.10 (dd, J=12.88, 3.03 Hz, 1 H) 4.99 (br. s., 2 H) 5.31 (d, J=2.02 Hz, 1 H) 5.83 (s, 1 H) 6.57 (ddd, J=7.07, 4.93, 0.88 Hz, 1 H) 6.62 - 6.67 (m, 1 H) 7.12 - 7.19 (m, 3 H) 7.45 (ddd, J=8.91, 7.01, 2.02 Hz, 1 H) 8.16 (ddd, J=4.93, 2.02, 0.88 Hz, 1 H).

Example 356

6-(2,3-Dimethylphenyl)-4-N-[(2-phenyl-2H-1,2,3-triazol-4-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (2-phenyl-2H-1,2,3-triazol-4-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 372; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.21 (s, 3 H) 2.28 (s, 3 H) 4.67 (br d, J=5.31 Hz, 2 H) 5.17 (br. s., 2 H) 5.58 - 5.70 (m, 1 H) 5.87 (s, 1 H) 7.08 - 7.18 (m, 3 H) 7.32 - 7.38 (m, 1 H) 7.45 - 7.51 (m, 2 H) 7.74 (s, 1 H) 8.01 - 8.06 (m, 2 H).

Example 357

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4-chlorobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-chlorobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 446; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.72 (quin, J=6.06 Hz, 2 H) 2.21 (s, 3 H) 2.30 (s, 3 H) 2.90 (d, J=5.05 Hz, 2 H) 3.49 (q, J=6.32 Hz, 2 H) 3.44 - 3.52 (m, 2 H) 5.33 - 5.43 (m, 1 H) 5.57 (br. s., 2 H) 5.78 (s, 1 H) 7.05 - 7.09 (m, 1 H) 7.09 - 7.13 (m, 1 H) 7.16 - 7.20 (m, 1 H) 7.41 - 7.46 (m, 2 H) 7.79 - 7.84 (m, 2 H).

Example 358

3-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-1-(4-chlorophenyl)urea.

Prepared according to general procedure 11 from 1-chloro-4-isocyanatobenzene and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 425; ^1H NMR (400 MHz, CD_3OD) δ ppm 1.85 (t, J=6.69 Hz, 2 H) 2.23 (s, 3

H) 2.34 (s, 3 H) 3.28 (overlap with methanol) 3.50 - 3.61 (m, 2 H) 5.97 (s, 1 H) 7.15 (s, 1 H) 7.17 - 7.25 (m, 3 H) 7.28 - 7.37 (m, 3 H).

Example 359

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3,5-dimethyl-1,2-oxazole-4-sulfonamide.

Prepared according to general procedure 10 from dimethyl-1,2-oxazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 431; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.79 (br. quin, J=6.0 Hz, 2 H) 2.23 (s, 3 H) 2.30 (s, 3 H) 2.42 (s, 3 H) 2.64 (s, 3 H) 3.01 (br. q, J=5.90 Hz, 2 H) 3.53 (br. q, J=6.00 Hz, 2 H) 5.89 (s, 1 H) 7.05 - 7.13 (m, 2 H) 7.18 - 7.21 (m, 1 H).

Example 360

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-2-(dimethylamino)acetamide.

In a vial 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (10 mg, 0.037 mmol) and 2-(dimethylamino)acetyl chloride hydrochloride (50 mg, 0.32 mmol) were suspended in DCM (1.0 ml), then Et_3N (0.013 ml, 0.092 mmol) was added. The resulting reaction mixture was stirred at r.t. for 1 h. Then MeOH was added and the mixture was stirred 30 min after which the mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 357; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.70 - 1.78 (m, 2 H) 2.28 (s, 3 H) 2.31 (s, 3 H) 2.35 (s, 6 H) 3.06 (s, 2 H) 3.34 - 3.41 (m, 2 H) 3.48 - 3.55 (m, 2 H) 5.85 (s, 1 H) 7.12 - 7.16 (m, 2 H) 7.17 - 7.22 (m, 1 H).

Example 361

3-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-1-(2,6-dichloropyridin-4-yl)urea.

Prepared according to general procedure 11 from 2,6-dichloro-4-isocyanatopyridine and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 460; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.86 (br. quint, J=6.7 Hz, 2 H) 2.24 (s, 3 H) 2.34 (s, 3 H) 3.30 - 3.34 (m [overlap w MeOH], 2H) 3.55 (br. s., 3 H) 5.98 (s, 1 H) 7.11 - 7.24 (m, 2 H) 7.27 - 7.33 (m, 1 H) 7.46 (s, 2 H).

Example 362

3-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-1-(3,4-difluorophenyl)urea.

Prepared according to general procedure 11 from 1,2-difluoro-4-isocyanatobenzene and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 427; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.81 - 1.89 (m, 2 H) 2.24 (s, 3 H) 2.34 (s, 3 H) 3.25 - 3.30 (m [overlap w MeOH], 2H) 3.55 (br. s., 2 H) 5.98 (s, 1 H) 6.94 - 7.01 (m, 1 H) 7.06 - 7.17 (m, 2 H) 7.17 - 7.23 (m, 1 H) 7.27 - 7.33 (m, 1 H) 7.45 - 7.54 (m, 1 H).

Example 363

N-[3-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propoxy)phenyl]acetamide.

Prepared according to general procedure 9 from N-[3-(3-aminopropoxy)phenyl]acetamide and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 406; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.96 (t, J=6.32 Hz, 2 H) 2.02 (s, 3 H) 2.15 (s, 3 H) 2.25 (s, 3 H) 4.00 (t, J=6.32 Hz, 2 H) 5.70 (s, 1 H) 5.92 (br. s., 2 H) 6.61 (dd, J=8.46, 1.64 Hz, 1 H) 6.85 - 6.99 (m, 1 H) 6.99 - 7.10 (m, 3 H) 7.11 - 7.19 (m, 2 H) 7.31 (s, 1 H) 9.88 (s, 1 H). A signal from one of the CH_2-groups is overlapping with solvent peaks and is not observed by NMR.

Example 364

6-(2,3-Dimethylphenyl)-4-N-[(2-methyl-1H-indol-5-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (2-methyl-1H-indol-5-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 358; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.22 (s, 3 H) 2.29 (s, 3 H) 2.45 (d, J=0.76 Hz, 3 H) 4.57 (br. s., 2 H) 5.16 - 5.32 (m, 2 H) 5.85 (s, 1 H) 6.18 - 6.21 (m, 1 H) 7.05 - 7.15 (m, 3 H) 7.15 - 7.19 (m, 1 H) 7.24 - 7.28 (m, 1 H) 7.47 (s, 1 H) 7.97 (br. s., 1 H).

Example 365

4-N-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(3,5-dimethyl-1H-pyrazol-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.17 (d, J=0.51 Hz, 3 H) 2.18 (s, 3 H) 2.21 (s, 3 H) 2.29 (s, 3 H) 2.51 - 2.63 (m, 1 H) 3.68 - 3.76 (m, 2 H) 4.13 (t, J=5.56 Hz, 2 H) 5.03 (s, 2 H) 5.37 - 5.47 (m, 1 H) 5.71 (s, 1 H) 5.77 (s, 1 H) 7.07 - 7.12 (m, 2 H) 7.12 - 7.17 (m, 1 H).

Example 366

6-(2,3-Dimethylphenyl)-4-N-[4-(pyrrolidin-1-yl)butyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-(pyrrolidin-1-yl)butan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.60 - 1.73 (m, 4 H) 1.78 - 1.86 (m, 4 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 2.49 - 2.60 (m, 6 H) 3.31 (br. s., 2 H) 4.79 (s, 2 H) 5.46 - 5.58 (m, 1 H) 5.78 (s, 1 H) 7.09 - 7.18 (m, 3 H).

Example 367

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-bromobenzamide.

4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 eq) was dissolved in THF (0.50 mL) and NMP (0.050 mL), then Et_3N (1.5 eq) and 3-bromobenzoyl chloride (1.2 eq) were added. The resulting reaction mixture was stirred at rt overnight. The mixture was then concentrated and purified by column chromatography. LCMS $[M+H]^+$ 454; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.80 - 1.89 (m, 2 H) 2.23 (s, 3 H) 2.30 (s, 3 H) 2.37 - 2.59 (m, 1 H) 3.47 - 3.58 (m, 4 H) 5.14 (br. s., 2 H) 5.55 - 5.69 (m, 1 H) 5.85 (s, 1 H) 7.07 - 7.13 (m, 2 H) 7.17 (dd, J=6.19, 2.91 Hz, 1 H) 7.31 (t, J=7.83 Hz, 1 H) 7.63 (ddd, J=7.89, 1.96, 1.01 Hz, 1 H) 7.75 (dd, J=7.83, 1.01 Hz, 1 H) 7.98 (t, J=1.77 Hz, 1 H).

Example 368

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzamide.

In a vial 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 eq) was dissolved in NMP (0.050 mL) and THF (0.50 mL), then Et_3N (1.5 eq) and benzoyl chloride (1.0 eq) were added. The resulting reaction mixture was stirred at rt for 1 h. The mixture was then concentrated and purified by column chromatography. LCMS $[M+H]^+$ 376; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.86 (t,

J=6.06 Hz, 2 H) 2.22 (s, 3 H) 2.29 (s, 3 H) 3.54 (dt, J=12.32, 6.09 Hz, 4 H) 5.36 - 5.54 (m, 1 H) 5.89 (s, 1 H) 6.14 - 6.31 (m, 1 H) 7.06 - 7.13 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.40 - 7.46 (m, 2 H) 7.47 - 7.53 (m, 1 H) 7.80 - 7.85 (m, 2 H).

Example 369

1-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-(propan-2-yl)urea.

Prepared according to general procedure 11 from 2-isocyanatopropane and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 357; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.12 (d, J=6.57 Hz, 6 H) 1.78 (t, J=6.69 Hz, 2 H) 2.24 (s, 3 H) 2.35 (s, 3 H) 3.20 (t, J=6.82 Hz, 2 H) 3.45 - 3.57 (m, 2 H) 3.74 - 3.85 (m, 1 H) 5.97 (s, 1 H) 7.19 (d, J=14.65 Hz, 2 H) 7.30 (s, 1 H).

Example 370

tert-Butyl N-(4-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}butyl)-carbamate.

Prepared according to general procedure 9 from tert-butyl N-(4-aminobutyl)carbamate. LCMS $[M+H]^+$ 386; ^{1}H NMR (400 MHz, $CDCl_3$) δ□ppm 1.45 (s, 9 H) 1.54 - 1.72 (m, 6 H) 2.24 - 2.28 (m, 3 H) 2.31 (s, 3 H) 3.20 (d, J=6.32 Hz, 3 H) 3.33 - 3.43 (m, 2 H) 4.79 - 4.91 (m, 1 H) 5.79 - 5.83 (m, 1 H) 7.14 (s, 2 H) 7.16 - 7.21 (m, 1 H).

Example 371

tert-Butyl N-(5-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}pentyl)-carbamate.

Step 1: 4-N-(5-Aminopentyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from pentane-1,5-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(5-Aminopentyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0.028 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.2 mg, 0.033 mmol) were dissolved in THF (0.50 mL). Then Et_3N (0.011 mL, 0.085 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[5-[[2-amino-6-(2,3-

dimethylphenyl)pyrimidin-4-yl]amino]pentyl]carbamate. LCMS $[M+H]^+$ 400; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.35 - 1.47 (m, 11 H) 1.52 (d, J=7.07 Hz, 2 H) 1.58 - 1.68 (m, 2 H) 2.24 (s, 3 H) 2.29 (s, 3 H) 3.13 (d, J=6.06 Hz, 2 H) 3.26 - 3.37 (m, 2 H) 4.58 - 4.68 (m, 1 H) 5.89 (s, 1 H) 7.11 (d, J=4.80 Hz, 2 H) 7.18 (d, J=4.80 Hz, 1 H).

Example 372

tert-Butyl N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}cyclohexyl)-carbamate.

Step 1: 4-N-(2-Aminocyclohexyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from cyclohexane-1,2-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(2-Aminocyclohexyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0.028 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.0 mg, 0.032 mmol) were dissolved in THF (0.50 mL). Then Et_3N (0.0050 mL, 0.036 mmol) was added and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]cyclohexyl]carbamate. LCMS $[M+H]^+$ 412; NMR: mixture of cis- and trans-diastereomers: ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 - 1.37 (m, 6 H) 1.38 - 1.42 (m, 18 H) 1.53 (br. s., 6 H) 1.79 (br. s., 4 H) 2.00 - 2.08 (m, 1 H) 2.18 - 2.23 (m, 1 H) 2.25 (d, J=3.79 Hz, 6 H) 2.31 (s, 6 H) 3.40 - 3.51 (m, 1 H) 3.62 - 3.75 (m, 1 H) 3.83 - 3.92 (m, 1 H) 3.97 - 4.10 (m, 1 H) 4.80 - 4.93 (m, 1 H) 4.97 - 5.10 (m, 1 H) 5.15 - 5.37 (m, 2 H) 5.43 - 5.67 (m, 2 H) 5.75 (s, 1 H) 5.83 (s, 1 H) 7.09 - 7.15 (m, 4 H) 7.16 - 7.21 (m, 2 H).

Example 373

tert-Butyl N-(1-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2-methylpropan-2-yl)carbamate.

Step 1: 4-N-(2-Amino-2-methyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from 2-methylpropane-1,2-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(2-Amino-2-methylpropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0,029 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.8 mg, 0.036 mmol) were dissolved in THF (0.50 mL). Then Et_3N (0.0061 mL, 0.044 mmol) was added and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-1,1-dimethyl-ethyl]carbamate. LCMS $[M+H]^+$ 386; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 (s, 6 H) 1.43 (s, 9 H) 2.26 (s, 3 H) 2.31 (s, 3 H) 3.53 (d, J=5.81 Hz, 2 H) 5.14 - 5.47 (m, 2 H) 5.87 (s, 1 H) 7.10 - 7.16 (m, 2 H) 7.18 (d, J=3.28 Hz, 1 H).

Example 374

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-cyanobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-cyanobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 437; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.70 - 1.82 (m, 4 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 2.98 (d, J=5.31 Hz, 2 H) 3.54 (d, J=5.81 Hz, 2 H) 4.71 - 4.80 (m, 1 H) 5.29 (br. s., 2 H) 5.76 (s, 1 H) 7.07 - 7.21 (m, 3 H) 7.59 - 7.65 (m, 1 H) 7.82 (dt, J=7.64, 1.36 Hz, 1 H) 8.14 (dq, J=7.96, 0.97 Hz, 1 H) 8.18 - 8.21 (m, 1 H).

Example 375

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 490; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.73 - 1.80 (m, 2 H) 2.23 (s, 3 H) 2.32 (s, 3 H) 2.95 - 3.01 (m, 2 H) 3.08 (s, 3 H) 3.51 - 3.58 (m, 2 H) 4.69 - 4.77 (m, 1 H) 5.31 (s, 2 H) 5.77 (s, 1 H) 7.08 - 7.21 (m, 3 H) 8.09 (q, J=8.76 Hz, 4 H).

Example 376

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzene-sulfonamide.

Prepared according to general procedure 10 from benzenesulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 412; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.72 (dt, J=12.06, 5.97 Hz, 2 H) 1.76 - 1.89 (m, 1 H) 2.22 (s, 3 H) 2.31 (s, 3 H) 2.93 (q, J=6.15 Hz, 2 H) 3.49 (q, J=6.40 Hz, 2 H) 4.70 - 4.82 (m, 1 H) 5.28 (br. s., 2 H) 5.72 - 5.74 (m, 1 H) 7.08 - 7.15 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.45 - 7.51 (m, 2 H) 7.52 - 7.57 (m, 1 H) 7.87 - 7.92 (m, 2 H).

Example 377

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)-3-fluorobenzene-1-sulfonamide.

Step 1: tert-butyl N-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)carbamate (prepared in example 239) (180 mg, 0.45 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred at reflux for 1 h. The TFA was evaporated and the crude residue was purified by silica gel chromatography using a gradient of 2-30% MeOH [containing 1 v/v% NH4OH] in DCM which afforded 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (110 mg, 0.37 mmol). LCMS $[M+H]^+$ 300.

Step 2: N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)-3-fluorobenzene-1-sulfonamide was prepared according to general procedure 10 from 3-fluorobenzene-1-sulfonyl chloride and 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (prepared in step 1) . LCMS $[M+H]^+$ 458; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (s, 6 H) 2.16 - 2.20 (m, 3 H) 2.29 (s, 3 H) 2.69 (d, J=7.07 Hz, 2 H) 3.38 (d, J=6.82 Hz, 2 H) 5.91 (s, 1 H) 6.53 (s, 1 H) 7.04 - 7.08 (m, 1 H) 7.09 - 7.15 (m, 1 H) 7.23 - 7.30 (m, 1 H) 7.38 - 7.45 (m, 1 H) 7.46 - 7.56 (m, 2 H) 7.64 (d, J=7.83 Hz, 1 H).

Example 378

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)-4-(morpholine-4-sulfonyl)benzene-1-sulfonamide.

Step 1: tert-butyl N-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)carbamate (prepared in example 239) (180 mg, 0.45 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred at reflux for 1 h. The TFA was evaporated and the crude residue was purified by silica gel chromatography

using a gradient of 2-30% MeOH [containing 1 v/v% NH4OH] in DCM which afforded 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (110 mg, 0.37 mmol). LCMS $[M+H]^+$ 300.

Step 2: N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}-2,2-dimethylpropyl)-4-(morpholine-4-sulfonyl)benzene-1-sulfonamide was prepared according to general procedure 10 from 4-(morpholine-4-sulfonyl)benzene-1-sulfonyl chloride and 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethyl-phenyl)pyrimidine-2,4-diamine (prepared in step 1 above). LCMS $[M+H]^+$ 589; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 0.92 (s, 6 H) 2.18 (d, J=0.51 Hz, 3 H) 2.28 (s, 3 H) 2.71 (d, J=6.82 Hz, 2 H) 2.99 - 3.06 (m, 4 H) 3.38 (d, J=6.82 Hz, 2 H) 3.70 - 3.78 (m, 4 H) 5.93 (s, 1 H) 6.94 (s, 1 H) 7.03 - 7.08 (m, 1 H) 7.09 - 7.15 (m, 1 H) 7.25 (d, J=7.58 Hz, 1 H) 7.42 (s, 1 H) 7.87 (d, J=8.59 Hz, 2 H) 8.02 (d, J=8.59 Hz, 2 H).

Example 379

6-(2,3-Dimethylphenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from prop-2-en-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.23 (s, 3 H) 2.31 (s, 3 H) 3.92 (br. s., 2 H) 4.95 (br. s., 3 H) 5.18 (dq, J=10.23, 1.47 Hz, 1 H) 5.26 (dq, J=17.18, 1.60 Hz, 1 H) 5.81 (s, 1 H) 5.85 - 5.96 (m, 1 H) 7.10 - 7.15 (m, 2 H) 7.15 - 7.19 (m, 1 H).

Example 380

1-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)imidazolidin-2-one.

Prepared according to general procedure 9 from 1-(3-aminopropyl)imidazolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 341.

Example 381

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-fluorobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-fluorobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 430.

Example 382
N-{4-[(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)sulfamoyl]-phenyl}acetamide.
Prepared according to general procedure 10 from 4-acetamidobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 469.

Example 383
N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)methanesulfonamide.
Prepared according to general procedure 10 from methanesulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 350.

Example 384
N-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-3-fluorobenzene-1-sulfonamide.
Prepared according to general procedure 10 from 3-fluorobenzene-1-sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 416.

Example 385
N-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-4-methoxybenzene-1-sulfonamide.
Prepared according to general procedure 10 from 4-methoxybenzene-1-sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 428.

Example 386
6-(2,3-Dimethylphenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 9 from prop-2-yn-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 253.

Example 387

2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}acetamide.
Prepared according to general procedure 9 from 2-aminoacetamide and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 272.

Example 388
N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4,5-dichlorothiophene-2-sulfonamide.
Prepared according to general procedure 10 from 4,5-dichlorothiophene-2-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 486.

Example 389
N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide.
Prepared according to general procedure 10 from 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)-pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 464.

Example 390
2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}acetonitrile.
Prepared according to general procedure 9 from 2-aminoacetonitrile and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 254.

Example 391
N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide.
Prepared according to general procedure 10 from 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 430; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.69 (s, 2 H), 7.33 - 7.38 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.16 - 7.20 (m, 1 H), 6.00 (s, 1 H), 3.71 (s, 3 H), 3.58 (s, 2 H), 3.06 (s, 2 H), 2.45 (s, 3 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 1.80 - 1.90 (m, 2 H).

Example 392

N-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide.
Prepared according to general procedure 10 from 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)-pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 450.

Example 393
4-N-{2-[(1,3-Benzoxazol-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 12 from 2-chloro-1,3-benzoxazole and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 375.

Example 394
6-(2,3-Dimethylphenyl)-4-N-(4-phenylbutan-2-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 9 from 4-phenylbutan-2-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 347.

Example 395
4-N-(2,2-Dimethyloxan-4-yl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 9 from 2,2-dimethyloxan-4-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 327.

Example 396
Ethyl 2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}acetate.
Prepared according to general procedure 9 from ethyl 2-aminoacetate and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 301.

Example 397
6-[(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-carbonitrile.
Prepared according to general procedure 12 from 6-chloropyridine-3-carbonitrile and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 360; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.32 - 8.34 (m, 1 H), 7.59 - 7.64 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 2 H), 7.15 - 7.18 (m, 1 H), 6.55 -

6.59 (m, 1 H), 5.97 (s, 1 H), 3.72 - 3.77 (m, 3 H), 3.66 - 3.71 (m, 3 H), 2.36 (s, 4 H), 2.24 (s, 3 H).

Example 398

4-N-{2-[(3-Bromo-1,2,4-thiadiazol-5-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 12 from 3-bromo-5-chloro-1,2,4-thiadiazole and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 420.

Example 399

6-(2,3-Dimethylphenyl)-4-N-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (5-methyl-4H-1,2,4-triazol-3-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 310; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.37 - 7.41 (m, 1 H), 7.25 - 7.30 (m, 1 H), 7.20 - 7.24 (m, 1 H), 6.12 (s, 1 H), 4.79 (s, 2 H), 2.47 (s, 3 H), 2.38 (s, 3 H), 2.29 (s, 3 H).

Example 400

6-(2,3-Dimethylphenyl)-4-N-{2-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 405.

Example 401

N-(2-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-4-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 476; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.10 - 8.14 (m, 3 H), 8.05 - 8.09 (m, 3 H), 7.16 - 7.20 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.05 - 7.08 (m, 1H), 5.73 - 5.76 (m, 1 H), 3.42 - 3.49 (m, 2 H), 3.14 (s, 6 H), 2.31 (s, 4 H), 2.18 (s, 3 H).

Example 402

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 490; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.43 - 8.45 (m, 1 H), 8.18 (ddd, J=7.8, 1.8, 1.0 Hz, 3 H), 8.11 (ddd, J=7.8, 1.8, 1.0 Hz, 3 H), 7.67 - 7.73 (m, 1 H), 7.15 - 7.19 (m, 1 H), 7.09 - 7.13 (m, 1 H), 7.08 (d, J=2.0 Hz, 1 H), 5.74 (s, 1 H), 5.31 (br. s., 2 H), 4.82 - 5.00 (m, 1 H), 3.50 (d, J=5.8 Hz, 2 H), 3.09 (s, 3 H), 2.94 (d, J=4.0 Hz, 2 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 1.71 (t, J=5.8 Hz, 2 H).

Example 403

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-2-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 2-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 490; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.20 - 8.33 (m, 3 H), 8.10 - 8.17 (m, 1 H), 7.84 - 7.90 (m, 5 H), 7.68 - 7.80 (m, 3 H), 7.16 - 7.21 (m, 3H), 7.12 (s, 3 H), 7.08 (d, J=1.5 Hz, 3 H), 5.74 (s, 3 H), 3.46 (s, 3 H), 3.43 (s, 8 H), 3.32 - 3.36 (m, 3 H), 3.07 (t, J=6.7 Hz, 5 H), 2.31 (s, 8 H), 2.19 (s, 3 H), 1.66 (t, J=6.7 Hz, 5 H).

Example 404

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(4-methylsulfonylphenyl)ethanamine (1.2 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 397.

Example 405

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0,08 mmol), 2-(4-methylthiazol-5-yl)ethanamine;dihydrobromide (1.2 equiv.) and N,N-diisopropylethylamine (4.25 equiv.) in n-butanol (0.3 ml) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 380.

Example 406

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 2-(4-methylthiazol-5-yl)ethanamine;dihydrobromide (1.2 equiv.) and N,N-diisopropylethylamine (4.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 360.

Example 407

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0,13 mmol), [2-(difluoromethyl)-4-pyridyl]methanamine;hydrochloride (1.2 equiv.) and N,N-diisopropylethylamine (3.25 equiv.) in n-butanol (0.3 ml) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 356.

Example 408

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), 2-(1H-imidazol-4-yl)ethanamine;dihydrochloride (1.2 equiv.) and N,N-diisopropylethylamine (3.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 309.

Example 409

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), 3-(1H-benzimidazol-2-yl)propan-1-amine (1.2 equiv.) and N,N-diisopropylethylamine (3.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 373.

Example 410

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.14 mmol), (1-methylbenzimidazol-2-yl)methanamine (1.2 equiv.) and N,N-diisopropylethylamine (1.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 359.

Example 411

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), (2-phenylthiazol-5-yl)methanamine hydrochloride (1.2 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 388.

Example 412

6-(3-chloro-2-methylphenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethanamine hydrochloride (1.2 equiv.) and N,N-diisopropylethylamine (3.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 344.

Example 413

6-(2,3-dichlorophenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.13 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethanamine hydrochloride (1.0 equiv.) and N,N-diisopropylethylamine (3.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 364.

Example 414

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

A mixture of 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 446.

Example 415

4-(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.13 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 equiv.) and N,N-diisopropyl-ethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 466.

Example 416

4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 equiv.) and N,N-diisopropylethylamine (2.25 equiv.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and

purified by preparative HPLC. LCMS $[M+H]^+$ 426.

Example 417

4-N-{1-[(4-Chlorophenyl)methyl]cyclopropyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (47 mg, 0.20 mmol), 1-[(4-chlorophenyl)methyl]cyclopropan-1-amine hydrochloride (52 mg, 0.24 mmol) and triethylamine (50 µL, 0.36 mmol) in n-butanol (3 mL) was heated in a sealed tube at 130°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 379.

Example 418

4-N-Cyclopropyl-6-(2,3,4-trichlorophenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine (21 mg, 0.050 mmol), cyclopropanamine (25 µL, 0.36 mmol) and triethylamine (25 µL, 0.18 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 329.

Example 419

4-N-[2-(4-Chlorophenyl)ethyl]-6-(2,3,4-trichlorophenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine (21 mg, 0.050 mmol), 2-(4-chlorophenyl)ethan-1-amine (30 µL, 0.24 mmol) and triethylamine (25 µL, 0.18 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 427.

Example 420

6-(2,3-dimethylphenyl)-4-N-($^2H_3$)methylpyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol) and d_3-methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 232.

Example 421

6-(2,3-dichlorophenyl)-4-N-($^2H_3$)methylpyrimidine-2,4-diamine.
A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.15 mmol) and d_3-methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC to afford the product. LCMS $[M+H]^+$ 272.

Example 422
6-(2-chloro-3-methylphenyl)-4-N-($^2H_3$)methylpyrimidine-2,4-diamine.
A solution of 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine (0.15 mmol) and d_3-methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC to afford the product. LCMS $[M+H]^+$ 252.

Example 423
4-N-[2-(4-Chlorophenyl)ethyl]-6-(1H-pyrrol-2-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine and (1-tert-butoxycarbonylpyrrol-2-yl)boronic acid. The t-butoxycarbonyl group was removed during work-up. LCMS $[M+H]^+$ 314; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.29 - 7.33 (m, 5 H), 7.27 (s, 2 H), 7.10 - 7.13 (m, 1 H), 6.88 - 6.92 (m, 1 H), 6.33 - 6.37 (m, 1 H), 6.12 (s, 1 H), 3.70 - 3.76 (m, 2 H), 2.91 - 2.96 (m, 2 H).

Example 424
N-(4-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}butyl)-4-methanesulfonylbenzene-1-sulfonamide.
Prepared according to general procedure 10 from 4-(methylsulfonyl)-benzenesulfonyl chloride and 4-N-(4-aminobutyl)-6-(2,3-dimethylphenyl)-pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 504; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.12 - 8.17 (m, 2 H), 8.06 - 8.10 (m, 2 H), 7.16 - 7.20 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.05 - 7.09 (m, 1 H), 5.76 - 5.79 (m, 1 H), 3.18 (s, 3 H), 2.94 - 2.99 (m, 2 H), 2.31 (s, 3 H), 2.19 (s, 3 H), 1.50 - 1.66 (m, 4 H).

Example 425

4-(2-{[2-amino-6-(4-fluoro-2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.
Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-fluoro-2,3-dimethyl-benzeneboronic acid. LCMS $[M+H]^+$ 416; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.81 - 7.85 (m, 2 H), 7.44 (d, J=8.6 Hz, 2 H), 7.07 (dd, J=8.5, 5.9 Hz, 1 H), 6.92 (t, J=8.8 Hz, 1 H), 5.75 (s, 1 H), 3.63 (br. s., 2 H), 2.99 (t, J=7.2 Hz, 2 H), 2.20 - 2.23 (m, 6 H).

Example 426
4-(2-{[2-amino-6-(3-cyano-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.
Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 3-cyano-2-methyl-benzeneboronic acid. LCMS $[M+H]^+$ 409; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.80 - 7.86 (m, 2 H), 7.70 (dd, J=7.8, 1.3 Hz, 1 H), 7.53 (d, J=6.8 Hz, 1 H), 7.37 - 7.47 (m, 3 H), 5.80 (s, 1 H), 3.65 (br. s., 2 H), 3.00 (t, J=7.2 Hz, 2 H), 2.49 (s, 3 H).

Example 427
4-(2-{[2-amino-6-(5-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.
Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 5-chloro-2-methyl-benzeneboronic acid. LCMS $[M+H]^+$ 418; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.81 - 7.85 (m, 2 H), 7.44 (d, J=8.3 Hz, 2 H), 7.21 - 7.29 (m, 3 H), 5.80 (s, 1 H), 3.64 (br. s., 2 H), 2.99 (t, J=7.2 Hz, 2 H), 2.28 (s, 3 H).

Example 428
4-(2-{[2-amino-6-(3,4-dichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.
Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 3,4-dichloro-2-methyl-benzeneboronic acid. LCMS $[M+H]^+$ 452; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (d, J=8.3 Hz, 2 H), 7.38 (d, J=8.3 Hz, 2 H), 7.33 - 7.36 (m, 1 H), 7.15 (s, 1 H),

5.73 (s, 1 H), 4.87 (s, 2 H), 4.81 - 4.84 (m, 2 H), 4.70 - 4.77 (m, 1 H), 3.61 - 3.69 (m, 2 H), 3.01 (s, 2 H), 2.41 (s, 3 H).

Example 429

6-(3-chloro-2-methylphenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from propargylamine and 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.40 - 7.43 (m, 1 H), 7.21 (s, 2 H), 5.85 - 5.88 (m, 1 H), 4.13 - 4.18 (m, 2 H), 2.59 (s, 1 H), 2.33 (s, 3 H).

Example 430

6-(4-fluoro-2,3-dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 4-fluoro-2,3-dimethyl-benzeneboronic acid. LCMS $[M+H]^+$ 415; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.88 (s, 2 H), 7.53 - 7.58 (m, 2 H), 7.06 - 7.11 (m, 1 H), 6.91 - 6.97 (m, 1 H), 5.76 (s, 1 H), 3.64 - 3.72 (m, 2 H), 3.11 (s, 3 H), 3.02 - 3.08 (m, 2 H), 2.22 - 2.25 (m, 6 H).

Example 431

6-(3,4-dichloro-2-methylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 3,4-dichloro-2-methyl-benzeneboronic acid. LCMS $[M+H]^+$ 451; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, J=8.6 Hz, 2 H), 7.57 (s, 2 H), 7.43 - 7.46 (m, 1 H), 7.17 - 7.21 (m, 1 H), 5.78 (s, 1 H), 3.63 - 3.75 (m, 2 H), 3.11 (s, 3 H), 3.03 - 3.08 (m, 2 H), 2.39 (s, 3 H).

Example 432

4-(2-{[2-amino-6-(4-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-chloro-2-methyl-benzene-boronic acid. LCMS $[M+H]^+$ 418; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.81 - 7.85

(m, 2 H), 7.42 - 7.46 (m, 2 H), 7.27 - 7.28 (m, 1 H), 7.23 (d, J=1.3 Hz, 2 H), 5.78 (s, 1 H), 3.63 (br. s., 2 H), 2.99 (t, J=7.1 Hz, 2 H), 2.30 (d, J=0.8 Hz, 3 H).

Example 433

4-(2-{[2-amino-6-(2-chloro-4-fluorophenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 2-chloro-4-fluoro-benzene-boronic acid. LCMS $[M+H]^+$ 422.

Example 434

4-(2-{[2-amino-6-(2,3,4-trifluorophenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 2,3,4-trifluorobenzeneboronic acid. LCMS $[M+H]^+$ 424.

Example 435

4-(2-{[2-amino-6-(4-fluoro-3-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-fluoro-3-methyl-benzene-boronic acid. LCMS $[M+H]^+$ 402; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.80 - 7.85 (m, 2 H), 7.67 - 7.72 (m, 1 H), 7.59 - 7.65 (m, 1 H), 7.41 - 7.46 (m, 2 H), 7.07 (dd, J=9.6, 8.6 Hz, 1 H), 6.12 (s, 1 H), 3.64 (t, J=7.2 Hz, 2 H), 2.99 (t, J=7.1 Hz, 2 H), 2.31 (d, J=2.0 Hz, 3 H).

Example 436

4-N-cyclopropyl-6-(4-fluoro-2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopropyl-pyrimidine-2,4-diamine and 4-fluoro-2,3-dimethyl-benzeneboronic acid. LCMS $[M+H]^+$ 273; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.08 - 7.15 (m, 1 H), 6.90 - 6.98 (m, 1 H), 5.90 - 6.07 (m, 1 H), 2.53 - 2.66 (m, 1 H), 2.21 - 2.26 (m, 6 H), 0.78 (dd, J=7.1, 2.0 Hz, 2 H), 0.54 (dd, J=3.7, 1.9 Hz, 2 H).

Example 437

3-[2-amino-6-(cyclopropylamino)pyrimidin-4-yl]-2-methylbenzonitrile.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopropyl-pyrimidine-2,4-diamine and 3-cyano-2-methyl-benzeneboronic acid. LCMS $[M+H]^+$ 266; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.73 - 7.77 (m, 1 H), 7.58 - 7.63 (m, 1 H), 7.42 - 7.48 (m, 1 H), 5.91 - 6.17 (m, 1 H), 2.59 - 2.70 (m, 1 H), 2.54 (s, 3 H), 0.81 (d, J=4.8 Hz, 2 H), 0.54 - 0.59 (m, 2 H).

Example 438

6-(2,3-dichlorophenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine and propargyl amine. LCMS $[M+H]^+$ 293.

Example 439

4-(2-{[2-amino-6-(4-fluoro-2,5-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 9 from 4-chloro-6-(4-fluoro-2,5-dimethyl-phenyl)pyrimidin-2-amine and 2-(4-sulfamoylphenyl)ethylammonium chloride. LCMS $[M+H]^+$ 416.

Example 440

4-N-[2-(3,5-dimethyl-1H-pyrazol-4-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and 2-(3,5-dimethyl-1H-pyrazol-1-ium-4-yl)ethylammonium dichloride. [M+H]+ 337; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.34 (s, 1 H), 7.21 - 7.26 (m, 1 H), 7.18 (dd, J=1.0, 0.5 Hz, 1 H), 6.00 (s, 1 H), 3.70 (t, J=6.8 Hz, 2 H), 2.83 (t, J=6.9 Hz, 2 H), 2.39 (s, 6 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

Example 441

4-N-{2-[(6-chloropyridazin-3-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 3,6-dichloropyridazine. [M+H]+ 370.

Example 442

2-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-4-carbonitrile.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 2-chloropyridine-4-carbonitrile. LCMS $[M+H]^+$ 360.

Example 443

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-sulfonamide.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 6-chloropyridine-3-sulfonamide. LCMS $[M+H]^+$ 414.

Example 444

1-N-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzene-1,4-disulfonamide.

Prepared according to general procedure 10 from 4-N-(4-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 4-(aminosulfonyl)benzenesulfonyl chloride. LCMS $[M+H]^+$ 491; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.04 - 8.08 (m, 2 H), 7.98 - 8.02 (m, 2 H), 7.28 (d, J=7.1 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.15 (d, J=1.5 Hz, 1 H), 5.91 (s, 1 H), 3.48 (d, J=1.5 Hz, 2 H), 2.98 (t, J=6.8 Hz, 2 H), 2.34 (s, 3 H), 2.22 (s, 3 H), 1.78 (t, J=6.8 Hz, 2 H).

Example 445

6-(2,3-dichlorophenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 2,3-dichlorobenzene-boronic acid. LCMS $[M+H]^+$ 437; ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.90 (d, J=8.6 Hz, 2 H), 7.78 (t, J=4.9 Hz, 1 H), 7.56 (d, J=8.6 Hz, 2 H), 7.49 (dd, J=4.9, 0.6 Hz, 2 H), 6.08 (s, 1 H), 3.84 (s, 2 H), 3.06 - 3.11 (m, 5 H).

Example 446

6-(2,3-dimethylphenyl)-4-N-[1-(1H-pyrazol-1-yl)propan-2-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)-pyrimidin-2-amine and 1-pyrazol-1-ylpropan-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.71 (d, J=7.8 Hz, 1 H), 7.57 (d, J=1.8 Hz, 1 H), 7.51 (d, J=2.3 Hz, 1 H), 7.24 (d, J=7.3 Hz, 1 H), 7.12 (t, J=7.6 Hz, 1 H), 7.04 - 7.08 (m, 1 H), 6.30 (t, J=2.3 Hz, 1 H), 5.85 (s, 1 H), 4.65 - 4.75 (m, 1 H), 4.34 - 4.41 (m, 1 H), 4.23 (dd, J=14.1, 6.3 Hz, 1 H), 2.29 (s, 3 H), 2.18 (s, 3 H), 1.16 (d, J=6.8 Hz, 3 H).

Example 447

6-(2,3-dimethylphenyl)-4-N-{2-[(3-methoxyphenyl)amino]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3-methoxyphenyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 364; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 - 7.26 (m, 1 H), 7.01 - 7.07 (m, 1 H), 6.96 - 7.00 (m, 1 H), 6.95 (t, J=2.0 Hz, 1 H), 6.84 (d, J=7.8 Hz, 1 H), 6.76 (dd, J=8.3, 2.0 Hz, 1 H), 5.91 (s, 1 H), 3.82 (d, J=4.8 Hz, 2 H), 3.75 (s, 3 H), 3.48 (br. s., 2 H), 2.24 (s, 3 H), 2.10 (s, 3 H).

Example 448

6-(2,3-dimethylphenyl)-4-N-{2-[(3-fluoro-4-methylphenyl)amino]ethyl}pyrimidine-2,4-diamine.

Step 1: A vial was charged with 2-fluoro-4-iodo-1-methyl-benzene (240 mg, 1.0 mmol), ethane-1,2-diamine (0.20 mL, 3.0 mmol), CuCl (9.9 mg, 0.10 mmol), and KOH (110 mg, 2.0 mmol). The vial was then flushed with nitrogen and sealed. The mixture was stirred at r.t. for 16 h, thereafter the mixture was extracted with EtOAc. The combined organic phases were dried, concentrated and purified by column chromatography to afford N'-(3-fluoro-4-methyl-phenyl)ethane-1,2-diamine.

Step 2: A mixture of 6-(2,3-dimethylphenyl)-4-chloropyrimidin-2-amine (30 mg, 0.13 mmol), N'-(3-fluoro-4-methyl-phenyl)ethane-1,2-diamine (20 mg, 0.12 mmol), and diisopropylethylamine (0.040 mL, 0.23 mmol) in 2-propanol (0.50 mL) was heated in a sealed tube at 150 °C for 30 min in a microwave reactor. The reaction

mixture was then concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 366; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.33 - 7.37 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.15 - 7.18 (m, 1 H), 6.93 - 6.99 (m, 1 H), 6.38 - 6.45 (m, 2 H), 5.99 (s, 1 H), 3.72 (s, 2 H), 3.39 (s, 2 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 2.11 (d, J=1.5 Hz, 3 H).

Example 449

4-N-{2-[(3,4-dichlorophenyl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3,4-dichlorophenyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 402; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.33 - 7.37 (m, 1 H), 7.24 (s, 1 H), 7.18 (m, 2 H), 6.76 (d, J=2.8 Hz, 1 H), 6.57 (dd, J=8.8, 2.8 Hz, 1 H), 5.97 (s, 3 H), 3.69 - 3.73 (m, 2 H), 3.37 - 3.42 (m, 2 H), 2.35 (s, 3 H), 2.23 (s, 3 H).

Example 450

4-N-{2-[(5-chloropyridin-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(5-chloro-2-pyridyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 369; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.61 - 7.69 (m, 2 H), 7.30 (d, J=7.6 Hz, 1 H), 7.10 - 7.22 (m, 3 H), 6.17 (br. s., 1 H), 3.71 (br. s., 4 H), 2.33 (s, 3 H), 2.24 (s, 3 H).

Example 451

4-N-{2-[(5-bromopyridin-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(5-bromo-2-pyridyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 413; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.07 (dd, J=2.3, 0.8 Hz, 1 H), 7.86 (dd, J=9.3, 2.3 Hz, 2 H), 7.33 - 7.37 (m, 2 H), 7.24 (t, J=7.6 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 6.90 (dd, J=9.5, 0.6 Hz, 1 H), 6.03 (s, 1 H), 3.77 - 3.82 (m, 2 H), 3.64 - 3.69 (m, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

Example 452

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]benzene-1-sulfonamide.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and 4-(2-aminoethylamino)benzene-sulfonamide. LCMS $[M+H]^+$ 413; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.64 (d, J=9.1 Hz, 2 H), 7.33 - 7.37 (m, 1 H), 7.24 (s, 1 H), 7.15 - 7.19 (m, 1 H), 6.70 (d, J=9.1 Hz, 2 H), 6.00 (s, 1 H), 3.72 - 3.77 (m, 2 H), 3.45 - 3.50 (m, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

Example 453

4-N-[2-(4-chlorophenyl)ethyl]-6-(dimethyl-1,2-oxazol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine and (3,5-dimethylisoxazol-4-yl)boronic acid. LCMS $[M+H]^+$ 344.

Example 454

6-(2,3-dimethylphenyl)-4-N-{2-[(pyridin-3-yl)amino]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3-pyridyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 335; ^1H NMR (400 MHz, CD_3OD) δ ppm 8.10 - 8.12 (m, 1 H), 7.97 - 8.00 (m, 1 H), 7.72 - 7.80 (m, 2 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.19 (dd, J=1.0, 0.5 Hz, 1 H), 6.04 (s, 1 H), 3.75 - 3.80 (m, 2 H), 3.54 (t, J=6.2 Hz, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 455

6-(3-chloro-2-methylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine

A solution of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (300 mg; 1.2 mmol) and the 2-(4-methylsulfonylphenyl)ethanamine (HCl salt) (300 mg; 1.27 mmol) in n-Butanol (2.0 ml) was treated with Hunigs base (400 mg; 3 mmol) and heated at 140 ° overnight. The mixture was purified by preparative HPLC (basic column to afford the product 390 mg. LCMS $[M+H]^+$ 417; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.89 (d, J= Hz, 2H), 7.56 (d, J= Hz, 2H), 7.44 - 7.41 (m, 1H), 7.25 - 7.18 (m, 2H), 5.79 (s, 1H), 3.68 (m, 2H), 3.11 (s, 3H), 3.07 – 3.03 (m, 2H) and 2.33 (s, 3H).

Example 456

[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-morpholino-methanone

The title compound was prepared according to general procedure 2 from intermediate 52 and (3-chloro-2-methyl-phenyl)boronic acid. $[M+H]^+$ 452.

Example 457

6-[(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)amino]pyridine-3-sulfonamide.

In a closed vial a mixture of intermediate 36 and 6-chloropyridine-3-sulfonamide (1.2 equiv.) were stirred neat at 150 °C for 16 h. The reaction mixture was purified by preparative LC. LCMS $[M+H]^+$ 428. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.34 - 8.37 (m, 2 H), 8.01 - 8.08 (m, 2 H), 7.35 - 7.41 (m, 2 H), 7.24 - 7.29 (m, 2 H), 7.19 - 7.24 (m, 3 H), 6.96 - 7.02 (m, 2 H), 6.04 (s, 1 H), 3.68 (s, 2 H), 3.55 (s, 2 H), 2.38 (s, 3 H), 2.27 (s, 3 H), 2.05 (s, 2 H).

Example 458

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-N-methylpyridine-3-sulfonamide

The title compound was prepared according to general procedure 12 from 6-chloro-N-methyl-pyridine-3-sulfonamide and intermediate 35. LCMS $[M+H]^+$ 428 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.36 - 8.39 (m, 1 H), 7.74 - 7.79 (m, 1 H), 7.33 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.15 - 7.19 (m, 1 H), 6.65 - 6.71 (m, 1 H), 5.96 - 5.99 (m, 1 H), 3.75 - 3.79 (m, 2 H), 3.68 - 3.73 (m, 2 H), 2.51 (s, 3 H), 2.35 - 2.37 (m, 2 H), 2.23 - 2.25 (m, 3 H).

Example 459

6-(2,3-dichlorophenyl)-4-N-{2-[(pyridin-4-yl)amino]ethyl}pyrimidine-2,4-diamine

Step 1: N'-(4-pyridyl)ethane-1,2-diamine was prepared according to general procedure 13 from 4-iodopyridine.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 21. LCMS $[M+H]^+$ 375. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.19 (dd, *J*=7.2, 1.1 Hz, 1 H), 8.04 (dd, *J*=7.1, 1.0 Hz, 1 H), 7.80 (dd, *J*=6.2, 3.4 Hz, 1 H), 7.48 – 7.51 (m, 2H), 7.03 (dd, *J*=7.2,

2.7 Hz, 1 H), 6.91 (dd, *J*=7.1, 2.8 Hz, 1 H), 6.18 (s, 1 H), 3.82 (dd, *J*=6.6, 6.0 Hz, 2 H), 3.69 (dd, *J*=6.6, 6.0 Hz, 2 H).

Example 460

4-(2-{[2-amino-6-(5-methylfuran-2-yl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 14 from intermediate 25 and potassium trifluoro(5-methylfuran-2-yl)boranuide. LCMS $[M+H]^+$ 374. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.86 (d, *J*=8.3 Hz, 2 H), 7.46 (d, *J*=8.3 Hz, 2 H), 7.15 (d, *J*=3.5 Hz, 1 H), 6.37 (dd, *J*=3.5, 1.0 Hz, 1 H), 6.25 (s, 1 H), 3.77 - 3.83 (m, 2 H), 3.02 - 3.07 (m, 2 H), 2.44 (s, 3 H).

Example 461

6-(3-chloro-2-methylphenyl)-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine

Prepared according to general procedure 3 from Intermediate 24 and 2-(4-chlorophenyl) ethanamine. LCMS $[M+H]^+$ 373; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.43 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.27 - 7.38 (m, 4 H), 7.21 - 7.26 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.03 (br. s., 1 H), 6.05 (br. s., 2 H), 5.72 (s, 1 H), 3.41 - 3.55 (m, 2 H), 2.82 (t, *J*=7.2 Hz, 2 H), 2.29 (s, 3 H).

Example 462

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-carboxamide

The title compound was prepared according to general procedure 12 from intermediate 35 and 6-chloropyridine-3-carboxamide. LCMS $[M+H]^+$ 378. 1H NMR (400 MHz, METHANOL-d4) δ ppm 8.49 (dd, J=2.3, 0.8 Hz, 1 H), 8.15 (dd, J=9.5, 1.9 Hz, 1 H), 7.36 (d, J=7.6 Hz, 1 H), 7.25 (t, J=7.5 Hz, 1 H), 7.14 - 7.19 (m, 1 H), 6.92 (d, J=8.8 Hz, 1 H), 6.02 (s, 1 H), 3.79 - 3.85 (m, 2 H), 3.70 - 3.75 (m, 2 H), 2.36 (s, 3 H), 2.24 (s, 3 H).

Example 463

4-N-methyl-6-(thiophen-3-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 14 from intermediate 20 and potassium trifluoro(3-thienyl)boranuide.

LCMS $[M+H]^+$ 207. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.10 (dd, *J*=2.9, 1.1 Hz, 1 H), 7.68 (dd, *J*=5.1, 2.9 Hz, 1 H), 7.51 (dd, *J*=5.1, 1.1 Hz, 1 H), 6.33 (s, 1 H), 3.02 (s, 3 H).

Example 464

4-N-methyl-6-(4-methylthiophen-2-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 14 from intermediate 20 and potassium trifluoro-(4-methyl-2-thienyl)boranuide.

LCMS $[M+H]^+$ 221. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 6.00 (s, 1 H), 5.84 (s, 1 H), 4.70 - 4.72 (m, 1 H), 1.48 (s, 3 H), 0.79 (d, *J*=1.0 Hz, 3 H).

Example 465

4-N-methyl-6-(1-methyl-1H-pyrazol-5-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 14 from intermediate 20 and potassium trifluoro(1-methyl-1H-pyrazol-5-yl)boranuide.

LCMS $[M+H]^+$ 205. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 7.41 (d, *J*=2.0 Hz, 1 H), 6.90 (br. s., 1 H), 6.56 (br. s., 1 H), 6.11 (br. s., 2 H), 6.01 (s, 1 H), 4.11 (s, 3 H), 2.77 (d, *J*=4.8 Hz, 3 H).

Example 466

4-N-{2-[(5-bromopyridin-2-yl)amino]ethyl}-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine

Step 1: A mixture of 5-bromo-2-chloro-pyridine and ethane-1,2-diamine was stirred at 90 °C for 16 h. The mixture was concentrated, diluted with KOH (2 M), and extracted with EtOAc x10. The combined organic extracts were concentrated and used in step 2 without further purification.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 21.

LCMS $[M+H]^+$ 453 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.06 (dd, *J*=2.3, 0.8 Hz, 1 H), 7.83 (dd, *J*=9.3, 2.3 Hz, 1 H), 7.77 - 7.80 (m, 1 H), 7.49 (d, *J*=6.8 Hz, 1 H), 7.49 (d, *J*=3.0 Hz, 1 H), 6.85 (d, *J*=9.3 Hz, 1 H), 6.15 (s, 1 H), 3.77 - 3.82 (m, 2 H), 3.63 - 3.68 (m, 2 H).

Example 467

4-N-methyl-6-(3-methyl-1H-pyrazol-4-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 14 from intermediate 20 and potassium trifluoro-(3-methyl-1H-pyrazol-4-yl)boranuide. LCMS $[M+H]^+$ 205.

Example 468

4-N-methyl-6-(1H-pyrrol-3-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 17 from intermediate 20 and triisopropoxy-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrrol-1-yl]silane. LCMS $[M+H]^+$ 190. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.46 (s, 1 H), 6.89 - 6.92 (m, 1 H), 6.54 - 6.57 (m, 1 H), 6.15 (s, 1 H), 2.99 (s, 3 H).

Example 469

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-2-methoxyacetamide

The title compound was prepared according to general procedure 15 from Intermediate 46 and 2-methoxyacetic. LCMS $[M+H]^+$ 398. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.80 (dd, *J*=5.8, 3.8 Hz, 1 H), 7.50 - 7.53 (m, 2 H), 6.13 (s, 1 H), 3.90 (s, 2 H), 3.57 (t, *J*=6.7 Hz, 2 H), 3.43 (s, 3 H), 3.30 - 3.35 (m, 2H, signal obscured by solvent), 1.66 (d, *J*=11.9 Hz, 4 H).

Example 470

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-2,2,2-trifluoroacetamide

The title compound was prepared according to general procedure 15 from Intermediate 46 and trifluoroacetic acid. LCMS $[M+H]^+$ 422. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.77 (dd, *J*=6.3, 3.5 Hz, 2 H), 7.48 - 7.51 (m, 2 H), 6.12 (s, 1 H), 3.56 (s, 2 H), 3.33 - 3.38 (m, 2 H), 1.67 (d, *J*=6.6 Hz, 5 H).

Example 471

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-4-methanesulfonylbenzamide

The title compound was prepared according to general procedure 15 from Intermediate 46 and 4-methylsulfonylbenzoic acid. LCMS $[M+H]^+$ 508. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.03 - 8.10 (m, 4 H), 7.80 (dd, *J*=5.3, 4.5 Hz, 1

H), 7.50 - 7.53 (m, 2 H), 6.13 (s, 1 H), 3.61 (s, 2 H), 3.47 - 3.53 (m, 2 H), 3.17 - 3.19 (m, 3 H), 1.71 - 1.81 (m, 4 H).

Example 472

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-1,2-oxazole-5-carboxamide

The title compound was prepared according to general procedure 15 from Intermediate 46 and isoxazole-5-carboxylic acid. LCMS $[M+H]^+$ 421. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.52 (d, *J*=1.8 Hz, 1 H), 7.77 - 7.80 (m, 1 H), 7.49 - 7.51 (m, 2 H), 6.94 - 6.95 (m, 1 H), 6.11 (s, 1 H), 3.55 - 3.60 (m, 2 H), 3.42 - 3.47 (m, 2 H), 1.69 - 1.75 (m, 5 H).

Example 473

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-3,4-dichlorobenzamide

A mixture of Intermediate 46 (1.0 equiv.), 3,4-dichlorobenzoyl chloride (1.3 equiv.), and diisopropylethylamine (5 equiv.) in DCM was stirred at 20 °C for 16 h. After completion the mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 498.

Example 474

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-2,2-dimethylpropanamide

A mixture of Intermediate 46 (1.0 equiv.), trimethylacetyl chloride (1.3 equiv.), and diisopropylethylamine (5 equiv.) in DCM was stirred at 20 °C for 16 h. After completion the mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 410. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.75 - 7.81 (m, 1 H), 7.50 (d, *J*=4.3 Hz, 2 H), 6.12 (s, 1 H), 3.54 (t, *J*=6.6 Hz, 2 H), 3.24 (t, *J*=6.6 Hz, 2 H), 1.54 - 1.70 (m, 4 H), 1.17 (s, 9 H).

Example 475

N-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-4-methanesulfonylbenzene-1-sulfonamide

The title compound was prepared according to general procedure 10 from Intermediate 46 and 4-methylsulfonylbenzenesulfonyl chloride. LCMS $[M+H]^+$

544. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.14 - 8.17 (m, 2 H), 8.07 - 8.10 (m, 2 H), 7.78 (dd, *J*=6.9, 2.7 Hz, 1 H), 7.49 - 7.52 (m, 2 H), 6.10 (s, 1 H), 3.49 (t, *J*=6.9 Hz, 2 H), 3.19 (s, 3 H), 2.97 (t, *J*=6.8 Hz, 2 H), 1.62 - 1.71 (m, 2 H), 1.52 - 1.61 (m, 2 H).

Example 476

3-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-1-[4-(methylsulfanyl)phenyl]urea

A mixture of intermediate 46 (1.0 equiv), 1-isocyanato-4-methylsulfanyl-benzene (1.1 equiv), and diisopropylethylamine (2.1 equiv) in acetonitrile was stirred at room temperature for 15 h. The mixture was concentrated and purified by preparative HPLC to afford the title compound. LCMS $[M+H]^+$ 491. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.74 - 7.79 (m, 1 H), 7.47 - 7.49 (m, 2 H), 7.28 - 7.32 (m, 2 H), 7.17 - 7.21 (m, 2 H), 6.11 (s, 1 H), 3.56 (t, *J*=6.8 Hz, 2 H), 3.26 (t, *J*=6.8 Hz, 2 H), 2.42 (s, 3 H), 1.66 - 1.75 (m, 2 H), 1.57 - 1.66 (m, 2 H).

Example 477

3-(4-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}butyl)-1-(4-methanesulfinylphenyl)urea

In a vial [4-(2,3-dichlorophenyl)-6-[4-[(4-methylsulfanylphenyl)carbamoylamino]butylamino]pyrimidin-2-yl]ammonium trifluoroacetate (from example 476) was dissolved in 2-propanol, then 0,2 ml H_2O_2 (30 wt%) was added and the resulting mixture was stirred 2 h at 20 °C. The crude mixture was then purified by preparative LC. LCMS $[M+H]^+$ 507.

Example 478

4-N-methyl-6-(2-methylfuran-3-yl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 17 from intermediate 20 and 4,4,5,5-tetramethyl-2-(2-methyl-3-furyl)-1,3,2-dioxaborolane. LCMS $[M+H]^+$ 205. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.56 (d, *J*=2.0 Hz, 1 H), 6.69 - 6.71 (m, 1 H), 6.09 (s, 1 H), 3.01 (s, 3 H), 2.50 (s, 3 H).

Example 479

4-N-methyl-6-[5-(pyrrolidin-1-ylmethyl)thiophen-2-yl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 17 from intermediate 20 and 1-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]methyl]pyrrolidine. LCMS $[M+H]^+$ 290. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.49 (d, *J*=3.5 Hz, 1 H), 6.98 (d, *J*=3.8 Hz, 1 H), 6.16 (s, 1 H), 3.84 (s, 2 H), 2.88 (s, 3 H), 2.57 - 2.65 (m, 4 H), 1.82 (dt, *J*=6.2, 3.0 Hz, 4 H).

Example 480

6-(4-fluoro-2,5-dimethylphenyl)-4-N-{2-[(5-nitropyridin-2-yl)amino]ethyl}pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from Intermediate 49 and N'-(5-nitro-2-pyridyl)ethane-1,2-diamine. LCMS $[M+H]^+$ 398. 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.01 (d, *J*=2.8 Hz, 1 H), 8.15 (dd, *J*=9.0, 2.7 Hz, 1 H), 7.15 (d, *J*=8.1 Hz, 1 H), 6.87 (d, *J*=10.6 Hz, 1 H), 6.37 (dd, *J*=9.3, 0.5 Hz, 1 H), 5.82 (s, 1 H), 5.12 - 5.24 (m, 1 H), 4.85 - 4.98 (m, 2 H), 2.31 (s, 3 H), 2.22 - 2.25 (m, 3 H), 1.73 - 1.84 (m, 1 H).

Example 481

[2-(2-amino-6-{[2-(4-chlorophenyl)ethyl]amino}pyrimidin-4-yl)phenyl]methanol

6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (intermediate 22) (30 mg, 0,11 mmol), 1,3-dihydro-2,1-benzoxaborol-1-ol (17 mg, 0,13 mmol), K_2CO_3 (53 mg, 0,38 mmol), Tetrakis(triphenylphosphine)palladium(0) (3,1 mg, 0,0030 mmol), MeCN (2 mL) and water (0,5 mL) were heated in the micro for 15 min at 120°C. The organic phase was filtered and purified by basic prep-HPLC to afford [2-(2-amino-6-{[2-(4-chlorophenyl)ethyl]amino}pyrimidin-4-yl)phenyl]methanol LCMS $[M+H]^+$ 355

Example 482

6-(3-chloro-2-methylphenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine (37 mg, 0.20 mmol; Intermediate 10), (3-chloro-2-methylphenyl)boronic acid (41 mg, 0.24 mmol), tetrakis(triphenylphosphine)palladium (0) (12 mg, 0.010 mmol) and potassium carbonate (55 mg, 0.40 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 1.5 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 275.

Example 483

6-(3-chloro-2-methylphenyl)-4-N-(2-fluoroethyl)pyrimidine-2,4-diamine.
Step 1: A mixture of 4,6-dichloropyrimidin-2-amine (164 mg, 1.00 mmol), 2-fluoroethan-1-amine hydrochloride (149 mg, 1.50 mmol) and triethylamine (300 µL, 2.15 mmol) in DMSO (4 mL) was heated at 160°C for 10 min using microwave irradiation. The reaction mixture was purified by preparative HPLC to afford 6-chloro-4-N-(2-fluoroethyl)pyrimidine-2,4-diamine; trifluoroacetic acid.
Step 2: A mixture of 6-chloro-4-N-(2-fluoroethyl)pyrimidine-2,4-diamine; trifluoroacetic acid (40 mg, 0.13 mmol), (3-chloro-2-methylphenyl)boronic acid (29 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium (0) (8 mg, 0.0070 mmol) and potassium carbonate (36 mg, 0.26 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 1 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 281; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (br. s., 1 H) 7.63 - 7.69 (m, 1 H) 7.37 - 7.43 (m, 2 H) 6.09 (s, 1 H) 4.51 - 4.71 (m, 2 H) 3.65 - 3.82 (m, 2 H) 2.30 (s, 3 H).

Example 484
6-(2,3-dimethylphenyl)-4-N-(2-fluoroethyl)pyrimidine-2,4-diamine.
A mixture of 6-chloro-4-N-(2-fluoroethyl)pyrimidine-2,4-diamine; trifluoroacetic acid (40 mg, 0.13 mmol; Example 483, Step 1), (2,3-dimethylphenyl)boronic acid (26 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium (0) (8 mg, 0.0070 mmol) and potassium carbonate (36 mg, 0.26 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 1 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 261.

Example 485
4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzoic acid.
A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0.10 mmol; Intermediate 24), 4-(2-aminoethyl)benzoic acid hydrochloride (30 mg, 0.15 mmol) and triethylamine (40 µL, 0.30 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 130°C overnight. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 383.

Example 486

4-(2-{[6-(2-acetylthiophen-3-yl)-2-aminopyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 14 from intermediate 25 and potassium (2-acetylthiophen-3-yl)trifluoroboranuide. LCMS $[M+H]^+$ 418. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.96 (d, *J*=5.1 Hz, 1 H), 7.84 - 7.88 (m, 2 H), 7.46 - 7.50 (m, 2 H), 7.39 (d, *J*=5.1 Hz, 1 H), 6.12 (s, 1 H), 3.82 (t, *J*=7.1 Hz, 2 H), 3.06 (t, *J*=7.1 Hz, 2 H), 2.62 (s, 3 H).

Example 487

3-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]-1H-pyrazol-1-yl}propanamide

The title compound was prepared according to general procedure 17 from intermediate 20 and 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]- propanamide. LCMS $[M+H]^+$ 262. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.11 (s, 1 H), 7.95 (s, 1 H), 6.09 (s, 1 H), 4.47 (t, *J*=6.7 Hz, 2 H), 2.90 - 2.92 (m, 3 H), 2.82 (t, *J*=6.7 Hz, 2 H).

Example 488

N-{6-[(2-{[2-amino-6-(4-fluoro-2,5-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridin-3-yl}acetamide

Step 1: In a flask 6-(4-fluoro-2,5-dimethyl-phenyl)-N4-[2-[(5-nitro-2-pyridyl)amino]ethyl]pyrimidine-2,4-diamine (from example 480) was dissolved in MeOH, then the flask was evacuated and the atmosphere was changed to H_2. The mixture was stirred at 20 °C for 16 h and then passed through a syringe filter and concentrated.

Step 2. The crude mixture from step 1 was dissolved in DCM, then Hünig's base (2.0 equiv) and acetyl chloride (1.1 equiv) were added and the mixture was stirred 3 h at 20 °C. Then the mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 410. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.50 (dd, *J*=2.5, 0.8 Hz, 1 H), 7.90 (dd, *J*=9.7, 2.4 Hz, 1 H), 7.28 (d, *J*=7.6 Hz, 1 H), 7.08 - 7.15 (m, 2 H), 6.07 (s, 1 H), 3.81 - 3.87 (m, 2 H), 3.67 - 3.73 (m, 2 H), 2.34 (s, 3 H), 2.28 - 2.31 (m, 3 H), 2.16 (s, 3 H).

Example 489

N-{6-[(2-{[2-amino-6-(4-fluoro-2,5-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridin-3-yl}methanesulfonamide

Step 1: In a flask 6-(4-fluoro-2,5-dimethyl-phenyl)-N4-[2-[(5-nitro-2-pyridyl)amino]ethyl]pyrimidine-2,4-diamine (from example 480) was dissolved in MeOH, then the flask was evacuated and the atmosphere was changed to H_2. The mixture was stirred at 20 °C for 16 h and then passed through a syringe filter and concentrated.

Step 2: The crude mixture from step 1 was dissolved in DCM, then Hünig's base (2.0 equiv) and methanesulfonyl chloride (1.1 equiv) were added and the mixture was stirred 3 h at 20 °C. Then the mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 446. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.84 - 7.88 (m, 2 H), 7.29 (d, *J*=7.3 Hz, 2 H), 7.08 - 7.13 (m, 5 H), 6.07 (s, 2 H), 3.81 - 3.86 (m, 2 H), 3.68 - 3.73 (m, 2 H), 3.04 (s, 3 H), 2.35 (s, 3 H), 2.29 - 2.32 (m, 3 H).

Example 490

6-(2,3-dimethylphenyl)-4-N-{2-[(6-methoxy-4-methylpyridin-3-yl)amino]ethyl}pyrimidine-2,4-diamine

Step 1: N'-(6-methoxy-4-methyl-3-pyridyl)ethane-1,2-diamine was prepared according to general procedure 13 from 5-bromo-2-methoxy-4-methyl-pyridine.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 379. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.55 (br. s., 1 H), 7.39 (d, *J*=7.6 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 7.19 - 7.23 (m, 1 H), 7.14 (br. s., 1 H), 6.05 (s, 1 H), 4.03 (s, 3 H), 3.81 (t, *J*=6.3 Hz, 2 H), 3.47 (t, *J*=6.3 Hz, 2 H), 2.38 (s, 3 H), 2.36 (s, 3 H), 2.27 (s, 3 H).

Example 491

6-(2,3-dimethylphenyl)-4-N-{2-[(6-methanesulfonylpyridin-3-yl)amino]ethyl}pyrimidine-2,4-diamine

Step 1: N'-(6-methylsulfonyl-3-pyridyl)ethane-1,2-diamine was prepared according to general procedure 13 from 5-bromo-2-methylsulfonyl-pyridine.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 413. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.13 (d, *J*=2.8 Hz, 1 H), 7.85 (dd, *J*=8.6, 0.5 Hz, 1 H), 7.38 (d, *J*=7.3 Hz, 1 H), 7.23 - 7.29 (m, 1 H), 7.15 - 7.21 (m, 2 H), 6.01

(s, 1 H), 3.75 - 3.80 (m, 2 H), 3.55 (t, *J*=6.2 Hz, 2 H), 3.12 (s, 3 H), 2.38 (s, 3 H), 2.26 (s, 3 H).

Example 492

5-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-sulfonamide

Step 1: 5-(2-aminoethylamino)pyridine-3-sulfonamide was prepared according to general procedure 13 from 5-bromopyridine-3-sulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 414. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.14 - 8.39 (m, 2 H), 7.78 (s, 1 H), 7.36 - 7.41 (m, 1 H), 7.24 - 7.29 (m, 1 H), 7.20 - 7.24 (m, 1 H), 6.01 (s, 1 H), 3.70 - 3.75 (m, 2 H), 3.52 - 3.57 (m, 2 H), 2.38 (s, 3 H), 2.27 (s, 3 H).

Example 493

[4-[2-[[2-amino-6-(3,5-dichloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-morpholino-methanone

The title compound was prepared according to general procedure 2 from intermediate 52 and (3,5-dichloro-2-methyl-phenyl)boronic acid.

$[M+H]^+$ 486.

Example 494

tert-butyl 4-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate.

Tetrakis(triphenylphosphine) palladium (0) (0.05 equiv.) was added after degassing with nitrogen to a stirred mixture of intermediate 33, tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.1 equiv.), potassium carbonate 1 M (2.5 equiv.) and dioxane in a tube. The tube was sealed and the reaction was heated at 80°C for 5 hours. The mixture was purified by preparative HPLC (acetonitrile/ammonium bicarbonate buffer) to give the title compound. LCMS [M+H]+ 474; 1H NMR (400 MHz, DMSO-d6) δ ppm 7.81 - 7.87 (m, 2 H), 7.49 - 7.55 (m, 2 H), 6.94 (br. s., 1 H), 6.62 (br. s., 1 H), 5.85 (s, 2 H), 5.77 (s, 1 H), 3.93 - 4.03 (m, 2 H), 3.42 - 3.54 (m, 4 H), 3.18 (s, 3 H), 2.92 (t, J=7.1 Hz, 2 H), 2.28 - 2.37 (m, 2 H), 1.41 (s, 9 H).

Example 495

4-[(1R,2S)-2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}cyclopropyl]benzene-1-sulfonamide.

Step 1: 6-chloro-N4-[(1S,2R)-2-phenylcyclopropyl]pyrimidine-2,4-diamine:

A mixture of 4,6-dichloropyrimidin-2-amine,(1S,2R)-2-phenylcyclopropanamine hydrochloride and N,N-Diisopropylethylamine in *n*-butanol was heated in a sealed tube at 80°C for 16 h. After cooling was the solid washed with ethanol to obtain the title product. LCMS $[M+H]^+$ 261.

Step 2: 4-[(1R,2S)-2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]cyclopropyl]benzenesulfonyl chloride:

To 6-chloro-N4-[(1S,2R)-2-phenylcyclopropyl]pyrimidine-2,4-diamine at 0 ^oC in DCM was chlorosulfonic acid added dropwise. The mixture was then stirred at rt for 2 h. The solution was poured into crushed ice, extracted with DCM. The combined organic phases were washed with water, dried, filtered, and concentrated to obtain the title compound. LCMS $[M+H]^+$ 359.

Step 3: 4-[(1R,2S)-2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]cyclopropyl]benzenesulfonamide:

Aqueous ammonia was added drop wise to a stirred, ice-chilled solution of 4-[(1R,2S)-2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]cyclopropyl]benzenesulfonyl chloride in acetonitrile. The resulting mixture was stirred for 20 min at RT and diluted with water, extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the title compound. LCMS $[M+H]^+$ 340.

Step 4: 4-[(1R,2S)-2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}cyclopropyl]benzene-1-sulfonamide was prepared according to general procedure 2 from 4-[(1R,2S)-2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]cyclopropyl]benzenesulfonamide and (3-chloro-2-methyl-phenyl)boronic acid. LCMS $[M+H]^+$ 430; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.69 (d, *J*=8.1 Hz, 2 H), 7.42 - 7.45 (m, 1 H), 7.40 (d, *J*=3.3 Hz, 1 H), 7.32 (d, *J*=8.3 Hz, 2 H), 7.15 - 7.28 (m, 4 H), 6.07 (s, 2 H), 5.71 (s, 1 H), 2.52 - 2.52 (m, 1 H), 2.28 (s, 3 H), 2.10 (ddd, *J*=8.8, 6.2, 3.2 Hz, 1 H), 1.28 - 1.42 (m, 2 H).

Example 496

4-N-[2-(4-methanesulfonylphenyl)ethyl]-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2,4-diamine.

To tert-butyl 4-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate was added 5 M HCl in dioxan and the mixture was stirred at rt for 20 min. The solvent was removed to obtain the title compound. LCMS $[M+H]^+$ 374.

Example 497

4-N-[2-(4-methanesulfonylphenyl)ethyl]-6-[1-(4-methylbenzenesulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 16 from N4-[2-(4-methylsulfonylphenyl)ethyl]-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-2,4-diamine hydrochloride and 4-methylbenzenesulfonyl chloride. LCMS $[M+H]^+$ 528. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.58 (br. s., 1 H), 8.85 (t, J=5.7 Hz, 1 H), 7.83 - 7.88 (m, 2 H), 7.67 - 7.72 (m, 2 H), 7.53 (d, J=8.3 Hz, 2 H), 7.46 (dd, J=8.5, 0.6 Hz, 2 H), 6.49 (br. s., 2 H), 5.97 (s, 1 H), 3.72 - 3.78 (m, 2 H), 3.57 - 3.69 (m, 2 H), 3.12 - 3.21 (m, 5 H), 2.97 (t, J=7.1 Hz, 2 H), 2.35 - 2.42 (m, 5 H).

Example 498

2-[3-(2-amino-6-{[2-(4-chlorophenyl)ethyl]amino}pyrimidin-4-yl)phenoxy]acetamide

4-N-[2-(4-chlorophenyl)ethyl]-6-iodopyrimidine-2,4-diamine (25 mg, 0,070 mmol), [3-(carbamoylmethoxy)phenyl]boronic acid (26 mg, 0,13 mmol), K_2CO_3 (55 mg, 0,40 mmol), Tetrakis(triphenylphosphine)palladium(0) (3,8 mg, 0,0030 mmol), MeCN (1,5 mL) and water (0,5 mL) were heated in the micro for 10 min at 120°C. The organic phase was filtered and purified by basic prep-HPLC to afford 2-[3-(2-amino-6-{[2-(4-chlorophenyl)ethyl]amino}pyrimidin-4-yl)phenoxy]acetamide. LCMS $[M+H]^+$ 398

Example 499

2-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyrimidine-4-carboxamide

The title compound was prepared according to general procedure 12 from intermediate 35 and 2-chloropyrimidine-4-carboxamide. LCMS $[M+H]^+$ 379. 1H

NMR (400 MHz, METHANOL-*d*4) δ ppm 8.49 (d, *J*=4.8 Hz, 1 H), 7.35 (d, *J*=7.3 Hz, 1 H), 7.19 - 7.26 (m, 2 H), 7.13 - 7.17 (m, 1 H), 5.94 (s, 1 H), 3.77 (s, 4 H), 2.35 (s, 3 H), 2.22 (s, 3 H).

Example 500

6-(2,3-dimethylphenyl)-4-N-{2-[(pyrazin-2-yl)amino]ethyl}pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 12 from intermediate 35 and 2-chloropyrazine. LCMS $[M+H]^+$ 336.

Example 501

4-N-{2-[(6-chloropyrimidin-4-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 12 from intermediate 35 and 4,6-dichloropyrimidine. LCMS $[M+H]^+$ 370. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.26 (s, 1 H), 7.36 (d, *J*=7.3 Hz, 1 H), 7.24 (t, *J*=7.6 Hz, 1 H), 7.17 (d, *J*=7.6 Hz, 1 H), 6.54 (br. s., 1 H), 5.97 (s, 1 H), 3.67 - 3.78 (m, 4 H), 2.36 (s, 3 H), 2.23 (s, 3 H).

Example 502

6-(3-chloro-2-methyl-phenyl)-N4-[3-(3-methylsulfonylanilino)propyl]pyrimidine-2,4-diamine

Step 1. A mixture of 1-bromo-3-methylsulfonyl-benzene (1.0 equiv.), CuCl (0.10 equiv.), KOH (2.0 equiv.), and 1,3-propanediamine (4.50 equiv.) were stirred at 90 °C for 16 h in a sealed vial. The mixture was allowed to cool and was then extracted with hot EtOAc ×5. The combined organics were concentrated and the excess of 1,3-propanediamine was removed by co-evaporation with toluene. The crude material was used without further purification.

Step 2. The title compound was prepared according to general procedure 9 from material from step 1 and intermediate 24. [M+H]+ 446. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.38 - 7.42 (m, 1 H), 7.28 - 7.34 (m, 1 H), 7.20 (d, *J*=7.6 Hz, 2 H), 7.11 (d, *J*=1.3 Hz, 2 H), 6.87 - 6.94 (m, 1 H), 5.82 (s, 1 H), 3.44 - 3.55 (m, 2 H), 3.21 - 3.27 (m, 3 H), 3.05 (s, 3 H), 2.31 (s, 3 H), 1.93 (t, *J*=6.8 Hz, 2 H).

Example 503

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzenecarbothioamide

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzonitrile (intermediate 53), O,O'-Diethyl dithiophosphate, and water was stirred at 20 °C for 2 days. The mixture was then diluted with water and extracted with DCM. The combined organics were purified by silica gel chromatography. LCMS $[M+H]^+$ 398.

Example 504

3-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)-N-tert-butylthiophene-2-sulfonamide

The title compound was prepared according to general procedure 14 from intermediate 33 and potassium [2-(tert-butylsulfamoyl)-3-thienyl]-trifluoro-boranuide. LCMS $[M+H]^+$ 510, 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.87 - 7.92 (m, 2 H), 7.64 - 7.67 (m, 2 H), 7.55 (d, *J*=8.3 Hz, 2 H), 6.31 (s, 1 H), 3.82 (t, *J*=7.1 Hz, 2 H), 3.10 (s, 3 H), 3.05 - 3.09 (m, 2 H), 1.28 (s, 9 H).

Example 505

tert-butyl N-{[5-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)thiophen-2-yl]methyl}carbamate

The title compound was prepared according to general procedure 14 from intermediate 33 and potassium [2-(tert-butylsulfamoyl)-3-thienyl]-trifluoro-boranuide. LCMS $[M+H]^+$ 504. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.89 (d, *J*=8.6 Hz, 2 H), 7.56 - 7.60 (m, 1 H), 7.54 (d, *J*=8.3 Hz, 2 H), 7.07 (d, *J*=3.8 Hz, 1 H), 6.19 (s, 1 H), 4.42 (s, 2 H), 3.79 (t, *J*=7.1 Hz, 2 H), 3.10 (s, 3 H), 3.06 (t, *J*=7.1 Hz, 2 H), 1.46 (s, 9 H).

Example 506

N-[4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]acetamide

The title compound was prepared according to general procedure 18 from Intermediate 50 and acetyl chloride. LCMS $[M+H]^+$ 376. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.46 - 7.51 (m, 2 H), 7.33 - 7.37 (m, 1 H), 7.20 - 7.26 (m, 3 H), 7.15 - 7.19 (m, 1 H), 5.96 (s, 1 H), 3.75 (t, *J*=7.2 Hz, 2 H), 2.91 (t, *J*=7.2 Hz, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H), 2.11 (s, 3 H).

Example 507

N-[4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]methanesulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 50 and methanesulfonyl chloride. LCMS $[M+H]^+$ 412. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.35 (d, *J*=7.1 Hz, 1 H), 7.14 - 7.28 (m, 6 H), 5.97 (s, 1 H), 3.76 (t, *J*=7.2 Hz, 2 H), 2.91 - 2.95 (m, 5 H), 2.36 (s, 3 H), 2.24 (s, 3 H).

Example 508

{2-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol

6-chloro-4-N-methylpyrimidine-2,4-diamine (20 mg, 0,13 mmol), 1,3-dihydro-2,1-benzoxaborol-1-ol (25 mg, 0,19 mmol), K_2CO_3 (78 mg, 0,57 mmol), Tetrakis(triphenylphosphine)palladium(0) (7,3 mg, 0,0060 mmol), MeCN (1,5 mL) and water (0,5 mL) were heated in the micro for 10 min at 120°C. The organic phase was filtered and purified by basic prep-HPLC to afford {2-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol. LCMS $[M+H]^+$ 231

Example 509

4-[2-({2-amino-6-[2-(hydroxymethyl)phenyl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide.

4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide (20 mg, 0,060 mmol), 1,3-dihydro-2,1-benzoxaborol-1-ol (12 mg, 0,090 mmol), K_2CO_3 (38 mg, 0,27 mmol), Tetrakis(triphenylphosphine)palladium(0) (3,5 mg, 0,0030 mmol), MeCN (1,5 mL) and water (0,5 mL) were heated in the micro for 10 min at 120°C. The organic phase was filtered and purified by basic prep-HPLC to afford 4-[2-({2-amino-6-[2-(hydroxymethyl)phenyl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide. LCMS $[M+H]^+$ 400

Example 510

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-N-methylbenzene-1-sulfonamide

Step 1: 4-(2-aminoethylamino)-N-methyl-benzenesulfonamide was prepared according to general procedure 13 from 4-iodo-N-methyl-benzenesulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 427. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.54 - 7.59 (m, 2 H), 7.33 - 7.37 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.15 - 7.20 (m, 1 H), 6.71 - 6.75 (m, 2 H), 5.98 (s, 1 H), 3.75 (t, *J*=6.2 Hz, 2 H), 3.49 (t, *J*=6.1 Hz, 2 H), 2.45 - 2.47 (m, 3 H), 2.36 (s, 3 H), 2.24 (s, 3 H).

Example 511

N-{4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-2-methylphenyl}acetamide

Step 1: N-[4-(2-aminoethylamino)-2-methyl-phenyl]acetamide was prepared according to general procedure 13 from N-(4-iodo-2-methyl-phenyl)acetamide.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 405. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.36 (d, *J*=7.6 Hz, 2 H), 7.22 - 7.28 (m, 3 H), 7.16 - 7.20 (m, 1 H), 6.92 (d, *J*=2.5 Hz, 1 H), 6.87 (dd, *J*=8.3, 2.5 Hz, 1 H), 6.03 (s, 1 H), 3.75 - 3.81 (m, 2 H), 3.55 (t, *J*=5.9 Hz, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 2.22 (s, 3 H), 2.14 (s, 3 H).

Example 512

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-3-one

Step 1: 6-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from (6-bromo-4H-1,4-benzoxazin-3-one.

Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 405. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.35 - 7.38 (m, 1 H), 7.25 (t, *J*=7.6 Hz, 1 H), 7.16 - 7.20 (m, 1 H), 6.93 (d, *J*=8.6 Hz, 1 H), 6.70 (dd, *J*=8.7, 2.7 Hz, 1 H), 6.65 (d, *J*=2.5 Hz, 1 H), 6.03 (s, 1 H), 4.53 (s, 2 H), 3.79 (t, *J*=6.1 Hz, 2 H), 3.53 (t, *J*=5.9 Hz, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 513

2-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]benzamide

Step 1: 2-(2-aminoethylamino)benzamide was prepared according to general procedure 13 from 2-bromobenzamide.
Step 2: The title compound was prepared according to general procedure 9 from the crude material in step 1 and intermediate 19. LCMS $[M+H]^+$ 377. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.57 (dd, *J*=7.8, 1.3 Hz, 1 H), 7.31 - 7.37 (m, 2 H), 7.22 - 7.27 (m, 1 H), 7.17 - 7.21 (m, 1 H), 6.83 (dd, *J*=8.3, 0.8 Hz, 1 H), 6.64 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1 H), 6.01 (s, 1 H), 3.79 (t, *J*=5.9 Hz, 2 H), 3.49 (t, *J*=5.9 Hz, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 514
2-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-4-carboxamide
The title compound was prepared according to general procedure 12 from intermediate 35 and 6-chloropyridine-3-carboxamide. LCMS $[M+H]^+$ 378.

Example 515
6-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethoxy)pyridine-3-carboxamide
A mixture of 2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethanol, 6-chloropyridine-3-carboxamide (1.5 equiv.) and potassium carbonate (3.5 equiv.) in DMSO was heated in a sealed tube at 90°C for 16 h. After cooling was methanol added to the solution, followed by filtration and purification by preparative HPLC acetonitrile/trifluoroacetic acid buffer to furnish the title compound. LCMS $[M+H]^+$ 379.

Example 516
N-[3-(2-amino-6-{[2-(4-methanesulfonylphenyl)ethyl]amino}pyrimidin-4-yl)-2-methylphenyl]-4-chloro-2-hydroxybenzamide
Prepared according to general procedure 2 from intermediate 33 and (4-chloro-2-hydroxy-N-[2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzamide. LCMS $[M+H]^+$ 552.

Example 517
3-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-1H-indol-5-ol

The title compound was prepared according to general procedure 9 from 3-(2-aminoethyl)-1H-indol-5-ol hydrogen chloride and intermediate 19. LCMS $[M+H]^+$ 374. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.16 (d, *J*=8.8 Hz, 1 H), 7.09 (t, *J*=7.4 Hz, 1 H), 6.95 - 7.06 (m, 3 H), 6.67 (dd, *J*=8.7, 2.4 Hz, 1 H), 5.75 (s, 1 H), 3.61 (br. s., 2 H), 2.96 (t, *J*=7.3 Hz, 2 H), 2.30 (s, 3 H), 2.17 (s, 3 H).

Example 518

4-N-{2-[5-(benzyloxy)-1H-indol-3-yl]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 5-benzyloxy tryptamine-HCl and intermediate 19. LCMS $[M+H]^+$ 464. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.37 - 7.43 (m, 2 H), 7.29 - 7.35 (m, 2 H), 7.24 - 7.28 (m, 1 H), 7.22 (d, *J*=8.8 Hz, 1 H), 7.09 - 7.16 (m, 2 H), 7.03 - 7.08 (m, 2 H), 7.00 (br. s., 1 H), 6.82 (dd, *J*=8.7, 2.4 Hz, 1 H), 5.74 (s, 1 H), 5.02 (s, 2 H), 3.60 (br. s., 2 H), 2.98 (t, *J*=7.0 Hz, 2 H), 2.27 (s, 3 H), 2.15 (s, 3 H).

Example 519

4-N-[2-(5-bromo-1H-indol-3-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 5-bromotryptamine-HCl and intermediate 19. LCMS $[M+H]^+$ 436. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.73 (s, 1 H), 7.22 - 7.26 (m, 1 H), 7.16 (dd, *J*=8.8, 1.9 Hz, 2 H), 7.06 - 7.13 (m, 2 H), 7.04 (br. s., 1 H), 5.74 (s, 1 H), 3.61 (br. s., 2 H), 2.99 (t, *J*=7.1 Hz, 2 H), 2.29 (s, 3 H), 2.17 (s, 3 H).

Example 520

6-(2,3-dimethylphenyl)-4-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 5-methoxytryptamine and intermediate 19. LCMS $[M+H]^+$ 388. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.21 (dd, *J*=8.8, 0.6 Hz, 1 H), 7.15 - 7.18 (m, 1 H), 7.10 (t, *J*=7.6 Hz, 1 H), 6.99 - 7.07 (m, 3 H), 6.74 (dd, *J*=8.8, 2.2 Hz, 1 H), 5.76 (s, 1 H), 3.77 (br. s, 3 H), 3.63 (br. s., 2 H), 3.01 (t, *J*=7.1 Hz, 2 H), 2.31 (s, 3 H), 2.17 (s, 3 H).

Example 521

6-(2,3-dimethylphenyl)-4-N-[2-(7-methyl-1H-indol-3-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 7-methyltryptamine and intermediate 19. LCMS $[M+H]^+$ 372.

Example 522

4-N-{2-[7-(benzyloxy)-1H-indol-3-yl]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 7-benzyloxytryptamine and intermediate 19. LCMS $[M+H]^+$ 464.

Example 523

6-(2,3-dimethylphenyl)-4-N-[2-(6-methoxy-1H-indol-3-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 6-methoxytryptamine and intermediate 19. LCMS $[M+H]^+$ 388. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.43 (d, *J*=8.8 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 7.10 (t, *J*=7.6 Hz, 1 H), 7.02 (br. s., 1 H), 6.96 (s, 1 H), 6.87 (d, *J*=2.5 Hz, 1 H), 6.67 (dd, *J*=8.5, 2.2 Hz, 1 H), 5.74 (s, 1 H), 3.80 (s, 3 H), 3.62 (br. s., 2 H), 3.00 (t, *J*=7.1 Hz, 2 H), 2.31 (s, 3 H), 2.18 (s, 3 H).

Example 524

6-(2,3-dichlorophenyl)-4-N-(2-methylcyclopropyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (41 mg, 0.15 mmol; Intermediate 21), 2-methylcyclopropan-1-amine (21 mg, 0.30 mmol) and triethylamine (50 µL, 0.36 mmol) in n-butanol (1 mL) was heated in a sealed tube at 95°C overnight. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 309.

Example 525

tert-butyl 4-(2-amino-6-{[2-(4-sulfamoylphenyl)ethyl]amino}pyrimidin-4-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate.

Tetrakis(triphenylphosphine) palladium (0) (0.05 equiv.) was added after degassing with nitrogen to a stirred mixture of intermediate 25, tert-butyl 4-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.1 equiv.), potassium carbonate 1 M (2.5 equiv.) and dioxane in a tube. The tube was sealed and the reaction was heated at 90°C for 3 hours. The mixture was purified by preparative HPLC (acetonitrile/ammonium bicarbonate buffer) to give the title compound. LCMS $[M+H]^+$ 475.

Example 526

4-(2-{[2-amino-6-(3-hydroxyphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from intermediate 25 and (3-hydroxyphenyl)boronic acid. LCMS $[M+H]^+$ 386.

Example 527

4-(2-{[2-amino-6-(cyclohept-1-en-1-yl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

Tetrakis(triphenylphosphine) palladium (0) (0.05 equiv.) was added after degassing with nitrogen to a stirred mixture of intermediate 25, 2-(cyclohepten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 equiv.), potassium carbonate 1 M (2.5 equiv.) and dioxane in a tube. The tube was sealed and the reaction was heated at 90°C for 16 hours. The mixture was purified by preparative HPLC (acetonitrile/ammonium bicarbonate buffer) to give the title compound. LCMS $[M+H]^+$ 388.

Example 528

ethyl 6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-carboxylate

Step 1. A mixture of ethyl 6-chloropyridine-3-carboxylate (1.0 equiv.) and ethane-1,2-diamine (1.1 equiv.) were stirred at 90 °C for 16h. The mixture was purified by preparative LC which afforded ethyl 6-(2-aminoethylamino)pyridine-3-carboxylate.

Step 2: The title compound was prepared according to general procedure 9 from ethyl 6-(2-aminoethylamino)pyridine-3-carboxylate and intermediate 19. LCMS $[M+H]^+$ 407. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.53 (dd, *J*=2.2, 0.6 Hz, 1 H), 8.23 (d, *J*=9.2 Hz, 1 H), 7.36 (d, *J*=7.6 Hz, 1 H), 7.24 (t, *J*=7.6 Hz, 1 H), 7.14 - 7.18 (m, 1 H), 7.01 (d, *J*=8.2 Hz, 1 H), 6.03 (s, 1 H), 4.37 (q, *J*=7.3 Hz, 2 H),

3.80 - 3.87 (m, 2 H), 3.73 - 3.79 (m, 2 H), 2.35 (s, 3 H), 2.23 (s, 3 H), 1.38 (t, *J*=7.1 Hz, 3 H).

Example 529

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-2-(trifluoromethyl)benzene-1-sulfonamide

Step 1: 4-(2-aminoethylamino)-2-(trifluoromethyl)benzenesulfonamide was prepared according to general procedure 13 from 4-bromo-2-(trifluoromethyl)benzenesulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 481. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.96 (d, *J*=8.8 Hz, 1 H), 7.35 (d, *J*=7.6 Hz, 1 H), 7.24 (t, *J*=7.7 Hz, 1 H), 7.14 - 7.19 (m, 1 H), 7.03 (d, *J*=2.5 Hz, 1 H), 6.85 (dd, *J*=9.2, 2.5 Hz, 1 H), 5.97 (s, 1 H), 3.71 - 3.79 (m, 2 H), 3.51 - 3.56 (m, 2 H), 2.35 (s, 3 H), 2.23 (s, 3 H).

Example 530

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]benzamide

Step 1: 4-(2-aminoethylamino)benzamide was prepared according to general procedure 13 from 4-iodobenzamide.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 377. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.66 - 7.72 (m, 2 H), 7.35 (d, *J*=7.6 Hz, 1 H), 7.23 (t, *J*=7.6 Hz, 1 H), 7.13 - 7.17 (m, 1 H), 6.64 - 6.69 (m, 2 H), 5.97 (s, 1 H), 3.75 (s, 2 H), 3.48 (s, 2 H), 2.35 (s, 3 H), 2.22 (s, 3 H).

Example 531

ethyl N-[4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]carbamate

The title compound was prepared according to general procedure 18 Intermediate 50 and ethyl chloroformate. LCMS $[M+H]^+$ 406. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.34 (d, *J*=8.5 Hz, 1 H), 7.16 (d, *J*=8.2 Hz, 2 H), 7.10 (t, *J*=7.6 Hz, 1 H), 7.02 - 7.06 (m, 1 H), 5.75 (s, 1 H), 4.17 (q, *J*=7.3 Hz, 2 H), 3.55

(br. s., 2 H), 2.84 (t, *J*=7.3 Hz, 2 H), 2.30 (s, 3 H), 2.18 (s, 3 H), 1.29 (t, *J*=7.1 Hz, 3 H).

Example 532

5-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-2-methoxybenzene-1-sulfonamide

Step 1: 5-(2-aminoethylamino)-2-methoxy-benzenesulfonamide was prepared according to general procedure 13 from 5-bromo-2-methoxy-benzenesulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 443. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.44 (d, *J*=2.8 Hz, 1 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.18 - 7.22 (m, 1 H), 7.07 - 7.11 (m, 1 H), 7.01 - 7.05 (m, 1 H), 6.00 (s, 1 H), 3.92 (s, 3 H), 3.70 (t, *J*=6.8 Hz, 2 H), 3.43 - 3.48 (m, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 533

tert-butyl 4-(2-amino-6-{[2-(4-sulfamoylphenyl)ethyl]amino}pyrimidin-4-yl)piperidine-1-carboxylate.

Palladium 10% on carbon was added to tert-butyl 4-[2-amino-6-[2-(4-sulfamoylphenyl)ethylamino]pyrimidin-4-yl]-3,6-dihydro-2H-pyridine-1-carboxylate in methanol. The solution was purged with N_2 for 5 minutes followed by dropwise addition of formic acid (3 equiv.) and the resulting mixture was stirred at 50 °C for 5 h. The mixture was then filtered and purified by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 477.

Example 534

4-{2-[(2-amino-6-cycloheptylpyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide.

Palladium 10% on carbon was added to 4-[2-[[2-amino-6-(cyclohepten-1-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide in methanol. The solution was purged with N_2 for 5 minutes followed by dropwise addition of formic acid (3 equiv.) and the resulting mixture was stirred at 90 °C for 4 h. The mixture was then filtered and purified by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 390.

Example 535

3-(2-amino-6-{[2-(4-sulfamoylphenyl)ethyl]amino}pyrimidin-4-yl)phenyl methanesulfonate.

To a dried tube was added 4-[2-[[2-amino-6-(3-hydroxyphenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide, dry THF and pyridine. The reaction mixture was then cooled to 0°C and methane sulfonyl chloride (1.1 equiv) was added dropwise. The reaction was stirred at RT for 16 h followed by quenching with water, filtration and purification by preparative HPLC. LCMS $[M+H]^+$ 464.

Example 536

3-(2-amino-6-{[2-(4-sulfamoylphenyl)ethyl]amino}pyrimidin-4-yl)phenyl trifluoromethanesulfonate

4-[2-[[2-amino-6-(3-hydroxyphenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide, N-phenylbis(trifluoromethane-sulfonimide), K_2CO_3, and THF were added to a tube and heated to 90 °C for 2 h. After cooling was methanol added to the solution followed by filtration and purification by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 518.

Example 537

4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzoic acid

The title compound was prepared according to general procedure 9 from intermediate 19 and 2-(4-carboxyphenyl)ethylammonium chloride.

LCMS $[M+H]^+$ 363.

Example 538

6-[(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-3-one

Step 1: 6-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-4H-1,4-benzoxazin-3-one.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 24. LCMS $[M+H]^+$ 425. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.61 (dd, *J*=7.7, 1.7 Hz, 1 H), 7.30 - 7.39 (m, 2 H), 6.90 (d, *J*=8.5 Hz, 1 H), 6.58 - 6.67 (m, 2 H), 6.06 (s, 1 H), 4.52 (s, 2 H), 3.79 (t, *J*=6.0 Hz, 2 H), 3.51 (t, *J*=6.0 Hz, 2 H), 2.38 (s, 3 H).

Example 539

6-(2,3-dimethylphenyl)-4-N-{2-[(2-methyl-1,3-benzothiazol-6-yl)amino]ethyl}pyrimidine-2,4-diamine

Step 1: N'-(2-methyl-1,3-benzothiazol-6-yl)ethane-1,2-diamine was prepared according to general procedure 13 from 6-iodo-2-methyl-1,3-benzothiazole.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 405. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.68 (d, *J*=8.8 Hz, 1 H), 7.34 (d, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=2.5 Hz, 1 H), 7.22 (t, *J*=7.6 Hz, 1 H), 7.11 (d, *J*=7.3 Hz, 1 H), 7.01 (dd, *J*=8.8, 2.2 Hz, 1 H), 5.97 (s, 1 H), 3.79 (t, *J*=6.0 Hz, 2 H), 3.53 (t, *J*=6.0 Hz, 2 H), 2.79 (s, 3 H), 2.34 (s, 3 H), 2.21 (s, 3 H).

Example 540

6-[(2-{[2-amino-6-(3-chlorophenyl)pyrimidin-4-yl]amino}ethyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-3-one

The title compound was isolated as a by-product from the reaction mixture in example 541 (step 2). LCMS $[M+H]^+$ 411. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.77 (t, *J*=1.9 Hz, 1 H), 7.62 - 7.67 (m, 2 H), 7.55 - 7.61 (m, 1 H), 6.87 - 6.97 (m, 2 H), 6.66 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.61 (d, *J*=2.5 Hz, 1 H), 6.35 (s, 1 H), 4.50 (s, 2 H), 3.79 (t, *J*=6.0 Hz, 2 H), 3.51 (t, *J*=6.0 Hz, 2 H).

Example 541

6-[(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)amino]-3,4-dihydro-2H-1,4-benzoxazin-3-one

Step 1: 6-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-4H-1,4-benzoxazin-3-one.

Step 2: The title compound was prepared according to general procedure 9 from the crude compound from step 1 and intermediate 21. LCMS $[M+H]^+$ 445. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.76 - 7.80 (m, 1 H), 7.48 - 7.51 (m, 2 H), 6.85 (d, *J*=8.5 Hz, 1 H), 6.52 (dd, *J*=8.7, 2.7 Hz, 1 H), 6.47(d, *J*=2.5 Hz, 1 H), 6.15 (s, 1 H), 4.49 (s, 2 H), 3.77 (t, *J*=6.0 Hz, 2 H), 3.45 (t, *J*=6.0 Hz, 2 H).

Example 542

6-(2,3-dichlorophenyl)-4-N-{2-[(2-methyl-1,3-benzothiazol-6-yl)amino]ethyl}pyrimidine-2,4-diamine

Step 1: N'-(2-methyl-1,3-benzothiazol-6-yl)ethane-1,2-diamine was prepared according to general procedure 13 from 6-iodo-2-methyl-1,3-benzothiazole.
Step 2: The title compound was prepared according to general procedure 9 from the crude compound from step 1 and intermediate 21. LCMS $[M+H]^+$ 445. ^1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.77 (dd, *J*=7.9, 1.6 Hz, 1 H), 7.63 (d, *J*=8.8 Hz, 1 H), 7.45 - 7.50 (m, 1 H), 7.42 (d, *J*=1.6 Hz, 1 H), 7.16 (d, *J*=2.2 Hz, 1 H), 6.93 (d, *J*=2.5 Hz, 1 H), 6.09 (s, 1 H), 3.77 - 3.81 (m, 2 H), 3.48 - 3.53 (m, 2 H), 2.76 (s, 3 H).

Example 543
6-(2,3-dimethylphenyl)-4-N-(2-{[4-(1H-1,2,3,4-tetrazol-5-yl)phenyl]amino}ethyl)pyrimidine-2,4-diamine
Step 1: N'-[4-(1H-tetrazol-5-yl)phenyl]ethane-1,2-diamine was prepared according to general procedure 13 from 5-(4-bromophenyl)-1H-tetrazole.
Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 402. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.73 - 7.78 (m, 2 H), 7.33 (s, 1 H), 7.17 - 7.23 (m, 1 H), 7.14 (d, *J*=0.9 Hz, 1 H), 6.77 - 6.82 (m, 2 H), 5.97 (s, 1 H), 3.77 (t, *J*=6.0 Hz, 2 H), 3.51 (t, *J*=6.0 Hz, 2 H), 2.33 (s, 3 H), 2.20 (s, 3 H).

Example 544
6-(2,3-dimethylphenyl)-4-N-{2-[(3-methanesulfonylphenyl)amino]ethyl}pyrimidine-2,4-diamine
Step 1: N'-(3-methylsulfonylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-3-methylsulfonyl-benzene.
Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 412.
1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.34 (s, 3 H), 7.23 (d, *J*=7.6 Hz, 1 H), 7.20 (d, *J*=1.3 Hz, 1 H), 7.14 (ddd, *J*=7.6, 1.9, 0.9 Hz, 1 H), 6.94 (ddd, *J*=8.2, 2.5, 0.9 Hz, 1 H), 5.99 (s, 1 H), 3.70 (s, 2 H), 3.48 (s, 2 H), 3.09 (s, 3 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 545
5-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-2-methoxybenzene-1-sulfonic acid

Step 1: 5-(2-aminoethylamino)-2-methoxy-benzenesulfonic acid was prepared according to general procedure 13 from 4-bromo-2-methoxy-benzenesulfonic acid.
Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 444.

Example 546
4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-3-fluorobenzene-1-sulfonamide
Step 1: 4-(2-aminoethylamino)-3-fluoro-benzenesulfonamide was prepared according to general procedure 13 from 4-bromo-3-fluoro-benzenesulfonamide.
Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 431.

Example 547
4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide.
Step 1: A mixture of 4,6-dichloropyrimidin-2-amine (600 mg, 3.66 mmol), 4-(2-aminoethyl)benzoic acid hydrochloride (812 mg, 4.02 mmol) and triethylamine (1.5 mL, 4.02 mmol) in n-butanol (20 mL) was heated in a sealed tube at 110°C overnight. The reaction mixture was concentrated and the crude material was recrystallized from a mixture of 2-propanol, methanol and water. The solid material was collected by filtration, washed with 2-propanol and dried under vacuum to afford 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzoic acid.

Step 2: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzoic acid (59 mg, 0.20 mmol), ammonia (1.0 mL, 0.50 mmol; as a 0.50 M solution in 1,4-dioxane), HATU coupling reagent (91 mg, 0.24 mmol) and triethylamine (in DMF (3 mL) was stirred at rt for 1.5 h. Purified by preparative HPLC to afford 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzamide.
Step 3: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzamide (27 mg, 0.093 mmol), (3-chloro-2-methylphenyl)boronic acid (21 mg, 0.12 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (12 mg, 0.010 mmol) and potassium carbonate (26 mg, 0.19 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 1 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 382; 1H NMR (400 MHz, CD_3OD) δ ppm 7.79 -

7.84 (2 H, m) 7.34 - 7.43 (3 H, m) 7.15 - 7.24 (2 H, m) 5.76 (1 H, s) 3.61 (2 H, s) 2.98 (2 H, t, J=7.11 Hz) 2.31 (3 H, s).

Example 548

4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

A mixture of 4-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl]benzoic acid (from example 537) and O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate was dissolved in DMF. Then NH3 in dioxane was added. The mixture was stirred at 20 °C for 4 h and then purified by preparative LC. LCMS $[M+H]^+$ 362. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.81 - 7.86 (m, 2 H), 7.34 - 7.41 (m, 4 H), 7.22 - 7.27 (m, 1 H), 7.15 - 7.20 (m, 1 H), 5.96 (s, 1 H), 3.81 (t, *J*=7.3 Hz, 2 H), 3.03 (t, *J*=7.1 Hz, 2 H), 2.36 (s, 3 H), 2.24 (s, 3 H).

Example 549

4-N-{2-[(2-amino-9H-purin-6-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

Step 1: N6-(2-aminoethyl)-9H-purine-2,6-diamine was prepared according to general procedure 13 from 6-bromo-9H-purin-2-amine.

Step 2: The title compound was prepared according to general procedure 9 from the compound from step 1 and intermediate 19. LCMS $[M+H]^+$ 391. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.04 (s, 1 H), 7.35 (d, *J*=7.3 Hz, 1 H), 7.23 (t, *J*=7.7 Hz, 1 H), 7.13 - 7.18 (m, 1 H), 5.99 (s, 1 H), 3.92 (d, *J*=6.0 Hz, 2 H), 3.82 - 3.89 (m, 2 H), 2.35 (s, 3 H), 2.22 (s, 3 H).

Example 550

4-(2-{[6-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-2-aminopyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

Prepared according to general procedure 16 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and acetyl chloride. LCMS $[M+H]^+$ 417.

Example 551

4-[2-({2-amino-6-[1-(2-methylpropanoyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and 2-methylpropanoyl chloride. LCMS $[M+H]^+$ 445.

Example 552

4-(2-{[2-amino-6-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and methanesulfonyl chloride. LCMS $[M+H]^+$ 453.

Example 553

4-[2-({2-amino-6-[1-(1,2-oxazole-5-carbonyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide.

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and isoxazole-5-carbonyl chloride. LCMS $[M+H]^+$ 470.

Example 554

4-(2-{[2-amino-6-(1-cyclopentanecarbonyl-1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and cyclopentanecarbonyl chloride. LCMS $[M+H]^+$ 471.

Example 555

4-[2-({2-amino-6-[1-(cyclopropanesulfonyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and cyclopropanesulfonyl chloride. LCMS $[M+H]^+$ 479.

Example 556

4-[2-({2-amino-6-[1-(2-cyclopentylacetyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and 2-cyclopentylacetyl chloride. LCMS $[M+H]^+$ 485.

Example 557

4-[2-({2-amino-6-[1-(4-methylbenzoyl)-1,2,3,6-tetrahydropyridin-4-yl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide

Prepared according to general procedure 16 from 4-[2-[[2-amino-6-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide hydrochloride and 4-methylbenzoyl chloride. LCMS $[M+H]^+$ 493. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.59 (br. s., 1 H), 8.70 - 8.94 (m, 1 H), 7.70 - 7.79 (m, 2 H), 7.45 (d, *J*=8.2 Hz, 2 H), 7.23 - 7.38 (m, 6 H), 6.60 (br. s., 2 H), 6.03 (s, 1 H), 4.14 - 4.41 (m, 2 H), 3.57 - 3.71 (m, 4 H), 2.94 (t, *J*=7.1 Hz, 2 H), 2.38 - 2.43 (m, 2 H), 2.35 (s, 3 H).

Example 558

N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]acetamide

The title compound was prepared according to General procedure 18 from Intermediate 47 and acetyl chloride. LCMS $[M+H]^+$ 396. 1H NMR (400 MHz, METHANOL-d4) δ ppm 7.63 (d, J=0.9 Hz, 1 H), 7.58 - 7.61 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.24 - 7.26 (m, 2 H), 7.02 (qd, J=2.8, 1.9 Hz, 1 H), 6.00 (s, 1 H), 3.78 (t, J=7.3 Hz, 2 H), 2.94 (t, J=7.3 Hz, 2 H), 2.37 (s, 3 H), 2.12 (s, 3 H).

Example 559

ethyl N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]carbamate

The title compound was prepared according to general procedure 18 from Intermediate 47 and ethyl chloroformate. LCMS $[M+H]^+$ 426. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.58 - 7.61 (m, 1 H), 7.45 - 7.48 (m, 1 H), 7.33 - 7.35 (m, 2 H), 7.16 - 7.24 (m, 3 H), 6.93 - 6.96 (m, 1H), 6.00 (s, 1 H), 4.13 - 4.20 (m, 2 H), 3.77 (s, 2 H), 2.93 (s, 2 H), 2.37 (s, 3 H), 1.30 (t, *J*=7.1 Hz, 3 H).

Example 560

6-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one

Step 1: 6-(2-aminoethyl)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 19 from 6-bromo-4H-1,4-benzoxazin-3-one.

Step 2: The title compound was prepared according to general procedure 9 from 6-(2-aminoethyl)-4H-1,4-benzoxazin-3-one and intermediate 24. LCMS $[M+H]^+$ 410. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.38 - 7.42 (m, 1 H), 7.19 - 7.23 (m, 1 H), 7.15 - 7.19 (m, 1 H), 6.86 (d, *J*=0.9 Hz, 2 H), 6.78 - 6.81 (m, 1 H), 5.73 - 5.77 (m, 1 H), 4.52 (s, 2 H), 3.52 - 3.61 (m, 2 H), 2.79 - 2.85 (m, 2 H), 2.31 (s, 3 H).

Example 561

4-N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 12 from intermediate 35 and intermediate 19. LCMS $[M+H]^+$ 455. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.34 - 7.39 (m, 2 H), 7.22 - 7.27 (m, 2 H), 7.15 - 7.20 (m, 2 H), 6.03 (s, 2 H), 3.81 - 3.84 (m, 4 H), 2.36 (s, 6 H), 2.25 (s, 6 H).

Example 562

methyl 5-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyrazine-2-carboxylate

The title compound was prepared according to general procedure 12 from intermediate 35 and methyl 5-chloropyrazine-2-carboxylate. LCMS $[M+H]^+$ 394. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.63 - 8.72 (m, 1 H), 7.86 - 7.97 (m, 1 H), 7.33 - 7.39 (m, 1 H), 7.20 - 7.27 (m, 1 H), 7.13 - 7.17 (m, 1 H), 5.93 - 5.96 (m, 1 H), 3.90 (s, 3 H), 3.73 - 3.81 (m, 4 H), 2.36 (s, 3 H), 2.23 (s, 3 H).

Example 563

methyl 2-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-6-methylpyrimidine-4-carboxylate

The title compound was prepared according to general procedure 12 from intermediate 35 and methyl 2-chloro-6-methyl-pyrimidine-4-carboxylate. LCMS $[M+H]^+$ 408. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.36 (d, *J*=7.3 Hz, 1 H),

7.24 (t, *J*=7.6 Hz, 1 H), 7.16 (d, *J*=6.6 Hz, 1 H), 7.12 (s, 1 H), 6.02 (s, 1 H), 3.91 (s, 3 H), 3.70 - 3.78 (m, 4 H), 2.40 (s, 3 H), 2.36 (s, 3 H), 2.24 (s, 3 H).

Example 564

4-N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 12 from intermediate 35 and 4-chloropyrimidin-2-amine. LCMS $[M+H]^+$ 351. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.57 (d, *J*=7.3 Hz, 1 H), 7.36 (d, *J*=7.6 Hz, 1 H), 7.25 (t, *J*=7.6 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 6.09 (d, *J*=7.3 Hz, 1 H), 6.01 (s, 1 H), 3.77 (m, 4 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 565

6-(2,3-dimethylphenyl)-4-N-{2-[(9H-purin-6-yl)amino]ethyl}pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 12 from intermediate 35 and 6-chloro-9H-purine. LCMS $[M+H]^+$ 376. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 8.46 (br. s., 1 H), 8.30 (s, 1 H), 7.35 (d, *J*=7.3 Hz, 1 H), 7.24 (t, *J*=7.6 Hz, 1 H), 7.13 - 7.18 (m, 1 H), 5.98 (s, 1 H), 4.01 (br. s., 2 H), 3.85 - 3.92 (m, 2 H), 2.35 (s, 3 H), 2.22 (s, 3 H).

Example 566

1-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-ethyl-urea

The title compound was prepared according to general procedure 21 from ethyl isocyanate and intermediate 48. LCMS $[M+H]^+$ 425.

Example 567

6-(3-chloro-2-methylphenyl)-4-N-[2-(3-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine

Step 1: 2-(3-methylsulfonylphenyl)ethanamine was prepared according to general procedure 19 from 1-bromo-3-methylsulfonyl-benzene.

Step 2: The title compound was prepared according to general procedure 9 from 2-(3-methylsulfonylphenyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 417. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.82 - 7.90 (m, 2 H), 7.65 - 7.70 (m,

1 H), 7.58 - 7.64 (m, 2 H), 7.35 - 7.38 (m, 2 H), 6.01 (s, 1 H), 3.86 (s, 2 H), 3.14 (s, 5 H), 2.38 (s, 3 H).

Example 568

5-N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)pyridine-2,5-diamine

Step 1: N-[5-(2-aminoethylamino)-2-pyridyl]acetamide was prepared according to general procedure 13 from N-(5-bromo-2-pyridinyl)acetamide.

Step 2: A mixture of the crude material from step 1 (2 equiv.), intermediate 19 (1 equiv.), and diisopropylethylamine (9 equiv.) in methanol was stirred at 150 °C for 1 h. The N-acetyl group was hydrolyzed under these reaction conditions and the title compound was isolated after preparative LC. LCMS $[M+H]^+$ 350. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.52 - 7.57 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.16 - 7.20 (m, 1 H), 7.13 (dd, *J*=2.8, 0.6 Hz, 1 H), 6.91 (dd, *J*=9.5, 0.6 Hz, 1 H), 6.04 (s, 1 H), 3.73 (t, *J*=6.5 Hz, 2 H), 3.30 – 3.35 (m, 2H, signal obscured by solvent), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 569

1-N-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-2-fluorobenzene-1,4-diamine

Step 1: N-[4-(2-aminoethylamino)-3-fluoro-phenyl]acetamide was prepared according to general procedure 13 from N-(4-bromo-3-fluorophenyl)acetamide.

Step 2: A mixture of the crude material from step 1 (2 equiv.), intermediate 19 (1 equiv.), and diisopropylethylamine (9 equiv.) in methanol was stirred at 150 °C for 1 h. The N-acetyl group was hydrolyzed under these reaction conditions and the title compound was isolated after preparative LC. LCMS $[M+H]^+$ 367.

Example 570

1-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-tert-butyl-urea

The title compound was prepared according to general procedure 21 from t-butyl isocyanate and intermediate 48. LCMS $[M+H]^+$ 453. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.57 - 7.62 (m, 1 H), 7.33 (d, *J*=1.9 Hz, 2 H), 7.23 - 7.27 (m, 2 H), 7.16 (s, 2 H), 5.99 (s, 1 H), 3.70 - 3.77 (m, 2 H), 2.85 - 2.91 (m, 2 H), 2.37 (s, 3 H), 1.34 - 1.38 (m, 9 H).

Example 571

1-allyl-3-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]urea

The title compound was prepared according to general procedure 21 from allyl isocyanate and intermediate 48. LCMS $[M+H]^+$ 437. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.59 (d, *J*=7.3 Hz, 1 H), 7.29 - 7.38 (m, 4 H), 7.17 (d, *J*=8.5 Hz, 2 H), 5.99 (s, 1 H), 5.83 - 5.95 (m, 1 H), 5.18 - 5.25 (m, 1 H), 5.11 (dd, *J*=10.4, 1.6 Hz, 1 H), 3.81 (dt, *J*=5.3, 1.6 Hz, 2 H), 3.74 (t, *J*=7.3 Hz, 2 H), 2.89 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H).

Example 572

ethyl N-[[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamoyl]carbamate

The title compound was prepared according to general procedure 21 from ethyl N-(oxomethylene)carbamate and intermediate 48. LCMS $[M+H]^+$ 469.

Example 573

1-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-sec-butyl-urea

The title compound was prepared according to general procedure 21 from *sec*-butyl isocyanate and intermediate 48. LCMS $[M+H]^+$ 453. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.59 (d, *J*=7.3 Hz, 1 H), 7.31 - 7.38 (m, 2 H), 7.26 - 7.31 (m, 2 H), 7.13 - 7.18 (m, 2 H), 5.99 (s, 1 H), 3.74 (t, *J*=7.3 Hz, 2 H), 3.65 - 3.72 (m, 1 H), 2.89 (t, *J*=7.3 Hz, 2 H), 2.37 (s, 3 H), 1.44 - 1.55 (m, 2 H), 1.15 (d, *J*=6.3 Hz, 3 H), 0.92 - 0.98 (m, 3 H).

Example 574

1-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-ethyl-thiourea

A mixture of intermediate 48 (1.0 equiv.) and ethyl isothiocyanate (2.4 equiv.) in DCM was stirred at 20 °C for 48 h. The reaction mixture was then concentrated and purified by preparative LC. LCMS $[M+H]^+$ 441.

Example 575

N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]morpholine-4-carboxamide

A mixture of intermediate 48 (1.0 equiv.), morpholine-4-carbonyl chloride, and diisopropylethylamine in DCM was stirred at reflux for 2 h. The mixture was then concentrated and purified by preparative LC. LCMS $[M+H]^+$ 467. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.60 (dd, *J*=7.4, 2.4 Hz, 1 H), 7.33 - 7.38 (m, 2 H), 7.29 - 7.32 (m, 2 H), 7.16 - 7.21 (m, 2 H), 5.99 (s, 1 H), 3.75 (t, *J*=7.3 Hz, 2 H), 3.68 - 3.72 (m, 4 H), 3.48 - 3.52 (m, 4 H), 2.91 (t, *J*=7.3 Hz, 2 H), 2.37 (s, 3 H).

Example 576

isopropyl N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was prepared according to general procedure 18 from intermediate 48 and isopropyl carbonochloridate. LCMS $[M+H]^+$ 440. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.44 - 7.49 (m, 1 H), 7.32 (d, *J*=7.9 Hz, 2 H), 7.07 - 7.25 (m, 4 H), 6.62 - 6.78 (m, 1 H), 6.37 (br. s., 1 H), 5.79 (s, 1 H), 5.00 (d, *J*=6.3 Hz, 1 H), 3.72 (d, *J*=6.0 Hz, 2 H), 2.87 (t, *J*=7.0 Hz, 3 H), 2.31 (s, 3 H), 1.27 - 1.34 (m, 6 H).

Example 577

Isobutyl N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was prepared according to general procedure 18 from intermediate 48 and isobutyl carbonochloridate. LCMS $[M+H]^+$ 454. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.45 - 7.49 (m, 1 H), 7.31 (d, *J*=7.6 Hz, 2 H), 7.11 - 7.22 (m, 5 H), 6.71 - 6.88 (m, 1 H), 6.44 (br. s., 1 H), 5.81 (s, 1 H), 3.94 (d, *J*=6.3 Hz, 2 H), 3.73 (d, *J*=6.0 Hz, 2 H), 2.87 (t, *J*=7.0 Hz, 2 H), 2.29 - 2.33 (m, 3 H), 1.97 (s, 1 H), 0.93 - 0.99 (m, 6 H).

Example 578

2,2-dimethylpropyl N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was prepared according to general procedure 18 from

intermediate 48 and 2,2-dimethylpropyl carbonochloridate. LCMS $[M+H]^+$ 468. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.45 (d, *J*=7.6 Hz, 1 H), 7.32 (d, *J*=7.6 Hz, 2 H), 7.09 - 7.20 (m, 4 H), 6.78 - 6.90 (m, 1 H), 6.61 - 6.69 (m, 1 H), 5.82 (s, 1 H), 3.85 (s, 2 H), 3.65 - 3.74 (m, 2 H), 2.86 (br. s., 2 H), 2.30 (s, 3 H), 0.93 - 0.99 (m, 9 H).

Example 579

2-methoxyethyl N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was prepared according to general procedure 18 from intermediate 48 and 2-methoxyethyl carbonochloridate. LCMS $[M+H]^+$ 456. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.45 (dd, *J*=7.6, 1.3 Hz, 1 H), 7.32 (d, *J*=8.2 Hz, 2 H), 7.10 - 7.21 (m, 4 H), 6.89 (s, 1 H), 6.36 (br. s., 1 H), 5.75 (s, 1 H), 4.29 - 4.35 (m, 2 H), 3.67 - 3.74 (m, 2 H), 3.63 - 3.67 (m, 2 H), 3.41 - 3.44 (m, 3 H), 2.87 (s, 2 H), 2.31 (s, 3 H).

Example 580

6-[2-[[2-amino-6-(3-chlorophenyl)pyrimidin-4-yl]amino]ethylamino]-3,3-dimethyl-4H-1,4-benzoxazin-2-one

The title compound was isolated as a side product from the experiment described in example 307. $[M+H]^+$ 439. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.75 - 7.77 (m, 1 H), 7.64 (dd, *J*=3.8, 1.9 Hz, 2 H), 7.56 - 7.61 (m, 1 H), 6.75 (d, *J*=8.8 Hz, 1 H), 6.36 - 6.41 (m, 1 H), 6.28 - 6.32 (m, 2 H), 3.74 (t, *J*=6.2 Hz, 2 H), 3.38 (t, *J*=6.0 Hz, 2 H), 1.40 (s, 6 H).

Example 581

6-(3-chloro-2-methylphenyl)-4-N-(2-methylcyclopropyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (38 mg, 0.15 mmol; Intermediate 24), 2-methylcyclopropan-1-amine (21 mg, 0.30 mmol) and triethylamine (50 µL, 0.36 mmol) in n-butanol (2 mL) was heated in a sealed tube at 95°C for 48 h. Concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 289.

Example 582

3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

Step 1: 3-(2-aminoethyl)benzenesulfonamide was prepared according to general procedure 19 from 3-bromobenzenesulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from 3-(2-aminoethyl)benzenesulfonamide and intermediate 24. LCMS $[M+H]^+$ 418.

Example 583

3-(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

Step 1: 3-(2-aminoethyl)benzenesulfonamide was prepared according to general procedure 19 from 3-bromobenzenesulfonamide.

Step 2: The title compound was prepared according to general procedure 9 from 3-(2-aminoethyl)benzenesulfonamide and intermediate 21. LCMS $[M+H]^+$ 438.

Example 584

But-2-ynyl N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was prepared according to general procedure 18 from intermediate 48 and but-2-ynyl carbonochloridate. LCMS $[M+H]^+$ 450. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.45 - 7.49 (m, 1 H), 7.32 (d, *J*=7.9 Hz, 2 H), 7.11 - 7.23 (m, 4 H), 6.83 (br. s., 1 H), 6.33 - 6.40 (m, 1 H), 5.80 (s, 1 H), 4.74 (dt, *J*=4.4, 2.2 Hz, 2 H), 3.73 (d, *J*=6.0 Hz, 2 H), 2.88 (t, *J*=7.0 Hz, 2 H), 2.29 - 2.34 (m, 3 H), 1.84 - 1.89 (m, 3 H).

Example 585

[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]cyanamide

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-N'-hydroxy-benzamidine (1.0 equiv.), 4-toluenesulfonyl chloride (1.1 equiv.), and diisopropylethylamine (1.1 equiv.) in DCM was stirred at 20 °C for 2 h. The mixture was then diluted with $NaHCO_3$ and extracted with DCM x3. The combined organics were concentrated and purified by silica gel chromatography. LCMS $[M+H]^+$ 379. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.39 - 7.44 (m, 1 H), 7.15 - 7.26 (m, 4 H), 6.91 (d, *J*=8.5 Hz, 2 H), 5.76 (br. s., 1

H), 3.50 - 3.65 (m, 2 H), 2.85 (s, 2 H), 2.31 (s, 3 H).

Example 586

6-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)pyridine-3-carboxamide

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol, 6-chloropyridine-3-carboxamide (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90 °C for 16 h. After cooling was methanol added to the solution followed by filtration and purification by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 399.

Example 587

6-[(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)amino]-2,2-dimethyl-3,4-dihydro-2H-1,4-benzoxazin-3-one

Step 1: 6-(2-aminoethylamino)-2,2-dimethyl-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-2,2-dimethyl-4H-1,4-benzoxazin-3-one

Step 2: The title compound was prepared according to general procedure 9 from 6-(2-aminoethylamino)-2,2-dimethyl-4H-1,4-benzoxazin-3-one and intermediate 24. LCMS $[M+H]^+$ 453. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.40 (dd, *J*=7.7, 1.7 Hz, 1 H), 7.14 - 7.23 (m, 2 H), 6.70 (d, *J*=8.5 Hz, 1 H), 6.28 - 6.34 (m, 1 H), 6.23 (d, *J*=2.5 Hz, 1 H), 5.80 (s, 1 H), 3.52 - 3.63 (m, 2 H), 3.27 (t, *J*=6.2 Hz, 2 H), 2.31 (s, 3 H), 1.40 (s, 6 H).

Example 588

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzamidine

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzenecarbothioamide and iodomethane (2.0 equiv.) in acetone was stirred at reflux for 2 h. Thereafter the mixture was concentrated and suspended in acetonitrile. Then ammonium acetate was added and the mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with MeOH and purified by preparative LC. LCMS $[M+H]^+$ 381. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.77 - 7.81 (m, 2 H), 7.59 - 7.64 (m, 1 H), 7.57 (d, *J*=8.5 Hz, 2 H), 7.31 - 7.39 (m, 2 H), 6.01 (s, 1 H), 3.79 - 3.86 (m, 2 H), 3.08 - 3.13 (m, 2 H), 2.38 (s, 3

H).

Example 589

4-N-(azetidin-3-yl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine

The title compound was isolated as a side product from the reaction mixture described in example 590. LCMS $[M+H]^+$ 270. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.16 - 7.20 (m, 1 H), 7.11 (t, *J*=7.4 Hz, 1 H), 7.04 - 7.08 (m, 1 H), 5.67 (s, 1 H), 4.28 (app. t, *J*=8.2 Hz, 2 H), 3.87 - 3.95 (m, 1 H), 3.75 (app. dd, *J*=9.2, 5.4 Hz, 2 H), 2.31 (s, 3 H), 2.18 (s, 3 H).

Example 590

tert-butyl 3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}azetidine-1-carboxylate

The title compound was prepared according to general procedure 9 from tert-butyl 3-aminoazetidine-1-carboxylate and intermediate 19. LCMS $[M+H]^+$ 370. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.16 - 7.20 (m, 1 H), 7.11 (t, *J*=7.6 Hz, 1 H), 7.04 - 7.08 (m, 1 H), 5.82 (s, 1 H), 4.65 - 4.74 (m, 1 H), 4.22 - 4.30 (m, 2 H), 3.77 - 3.84 (m, 2 H), 2.31 (s, 3 H), 2.19 (s, 3 H), 1.45 (s, 9 H).

Example 591

2-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)pyrimidine-4-carboxamide

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol, 2-chloropyrimidine-4-carboxamide (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90 °C for 16 h. After cooling was methanol added to the solution followed by filtration and purification by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 400. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.78 (d, *J*=5.1 Hz, 1 H), 7.68 (d, *J*=5.1 Hz, 1 H), 7.40 (dd, *J*=7.4, 1.7 Hz, 1 H), 7.16 - 7.24 (m, 2 H), 5.82 (br. s., 1 H), 4.67 (t, *J*=5.5 Hz, 2 H), 3.73 - 3.92 (m, 2 H), 2.31 (s, 3 H).

Example 592

2-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)pyrimidine-4-carboxylic acid.

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-

yl]amino]ethanol, 2-chloropyrimidine-4-carboxamide (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90 °C for 16 h. After cooling was methanol added to the solution followed by filtration and purification by preparative HPLC to give the title compound. LCMS $[M+H]^+$ 401. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.63 (br. s., 1 H), 7.50 (dd, *J*=6.6, 2.5 Hz, 2 H), 7.16 - 7.37 (m, 2 H), 6.00 (s, 1 H), 4.61 - 4.71 (m, 2 H), 3.89 (br. s., 2 H), 2.34 (s, 3 H).

Example 593

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-2,2-dimethylpropanamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and 2,2-dimethylpropanoyl chloride. LCMS $[M+H]^+$ 438. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.42 - 7.47 (m, 2 H), 7.41 (dd, *J*=7.4, 1.4 Hz, 1 H), 7.14 - 7.24 (m, 4 H), 5.76 (s, 1 H), 3.50 - 3.66 (m, 2 H), 2.83 - 2.91 (m, 2 H), 2.31 (s, 3 H), 1.29 (s, 9 H).

Example 594

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-2,2,2-trifluoroethane-1-sulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and 2,2,2-trifluoroethanesulfonyl chloride. LCMS $[M+H]^+$ 500. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.58 - 7.62 (m, 1 H), 7.31 - 7.38 (m, 2 H), 7.26 - 7.31 (m, 2 H), 7.20 - 7.25 (m, 2 H), 6.00 (s, 1 H), 4.07 (q, *J*=9.5 Hz, 2 H), 3.77 (t, *J*=7.1 Hz, 2 H), 2.94 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H).

Example 595

1-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-3-(propan-2-yl)urea

A mixture of Intermediate 48 and isopropyl isocyanate were stirred in DCM at 20 °C for 24 h. The desired compound precipitated and the solid was filtered off and washed with DCM. LCMS $[M+H]^+$ 439. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.38 - 7.43 (m, 1 H), 7.24 - 7.29 (m, 2 H), 7.11 - 7.24 (m, 4 H), 5.75 (s, 1 H), 3.87 (dt, *J*=13.0, 6.6 Hz, 1 H), 3.52 - 3.62 (m, 2 H), 2.83 (t, *J*=7.3 Hz, 2 H), 2.31 (s, 3 H), 1.17 (d, *J*=6.6 Hz, 6 H).

Example 596

tert-butyl N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]carbamate

The title compound was prepared according to general procedure 18 from Intermediate 48 and di-tert-butyl dicarbonate. LCMS $[M+H]^+$ 454. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.38 - 7.43 (m, 1 H), 7.31 (d, *J*=8.5 Hz, 2 H), 7.12 - 7.24 (m, 4 H), 5.75 (s, 1 H), 3.49 - 3.63 (m, 2 H), 2.83 (s, 2 H), 2.31 (s, 3 H), 1.49 - 1.53 (m, 9 H).

Example 597

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]cyclopropanecarboxamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and cyclopropanecarbonyl chloride. LCMS $[M+H]^+$ 422. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.44 - 7.49 (m, 2 H), 7.41 (dd, *J*=7.6, 1.3 Hz, 1 H), 7.14 - 7.24 (m, 4 H), 5.75 (s, 1 H), 3.58 (br. s., 2 H), 2.86 (t, *J*=7.3 Hz, 2 H), 2.31 (s, 3 H), 1.75 (tt, *J*=7.9, 4.7 Hz, 1 H), 0.91 - 0.96 (m, 2 H), 0.81 - 0.87 (m, 2 H).

Example 598

6-(2,3-dimethylphenyl)-4-N-[2-(thiophen-2-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from intermediate 19 and 2-(2-thienyl)ethanamine. LCMS $[M+H]^+$ 325. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.36 (d, *J*=7.6 Hz, 1 H), 7.22 - 7.27 (m, 2 H), 7.16 - 7.21 (m, 1 H), 6.93 - 6.97 (m, 1 H), 6.90 - 6.93 (m, 1 H), 5.99 (s, 1 H), 3.79 (t, *J*=7.1 Hz, 2 H), 3.16 - 3.21 (m, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

Example 599

6-(3-chloro-2-methylphenyl)-4-N-[2-(3,4-dichlorophenyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from intermediate 24 and 2-(3,4-dichlorophenyl)ethanamine. LCMS $[M+H]^+$ 407. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.58 - 7.62 (m, 1 H), 7.44 - 7.47 (m, 2 H), 7.31 - 7.38 (m, 2 H), 7.21 - 7.24 (m, 1 H), 5.99 (s, 1 H), 3.75 - 3.81 (m, 2 H), 2.92 - 2.98 (m, 2 H), 2.37 (s, 3 H).

Example 600

6-(3-chloro-2-methylphenyl)-4-N-[2-(2,4-dichlorophenyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from intermediate 24 and 2-(2,4-dichlorophenyl)ethanamine. LCMS $[M+H]^+$ 407. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.58 - 7.63 (m, 1 H), 7.47 (d, *J*=1.9 Hz, 1 H), 7.27 - 7.38 (m, 4 H), 5.98 (s, 1 H), 3.80 (t, *J*=7.0 Hz, 2 H), 3.10 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H).

Example 601

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]ethane-1-sulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and ethanesulfonyl chloride. 1H NMR (400 MHz, METHANOL-*d*4) δ ppm 7.57 - 7.61 (m, 1 H), 7.31 - 7.37 (m, 2 H), 7.22 - 7.26 (m, 2 H), 7.18 - 7.22 (m, 2 H), 6.00 (s, 1 H), 3.76 (t, *J*=7.1 Hz, 2 H), 3.05 (q, *J*=7.4 Hz, 2 H), 2.92 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H), 1.26 - 1.32 (m, 3 H).
LCMS $[M+H]^+$ 446.

Example 602

4-(2-{[2-amino-6-(2,4,5-trimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (2,4,5-trimethylphenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 412.

Example 603

4-(2-{[2-amino-6-(4-methoxy-2,5-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (4-methoxy-2,5-dimethyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 428.

Example 604

4-(2-{[2-amino-6-(4,5-dichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (4,5-dichloro-2-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 452.

Example 605

4-(2-{[2-amino-6-(5-chloro-4-methoxy-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (5-chloro-4-methoxy-2-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 448.

Example 606

4-(2-{[2-amino-6-(1H-indol-4-yl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from 1H-indol-4-ylboronic acid and intermediate 25. LCMS $[M+H]^+$ 409.

Example 607

4-(2-{[2-amino-6-(2,5-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (2,5-dimethylphenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 398.

Example 608

4-(2-{[2-amino-6-(5-fluoro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (5-fluoro-2-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 402.

Example 609

4-(2-{[2-amino-6-(3,4,5-trichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (3,4,5-trichloro-2-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 486.

Example 610

4-(2-{[2-amino-6-(5-chloro-2-fluoro-3-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (5-chloro-2-fluoro-3-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 436.

Example 611

4-(2-{[2-amino-6-(3,5-dichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide

The title compound was prepared according to general procedure 2 from (3,5-dichloro-2-methyl-phenyl)boronic acid and intermediate 25. LCMS $[M+H]^+$ 452.

Example 612

4-(2-{[2-amino-6-(3,4,5-trichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (3,4,5-trichloro-2-methyl-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 450.

Example 613

4-(2-{[2-amino-6-(3,5-dichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (3,5-dichloro-2-methyl-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 416.

Example 614

4-(2-{[2-amino-6-(4-fluoro-2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (4-fluoro-2,3-dimethyl-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 380.

Example 615

4-(2-{[2-amino-6-(3,4-dichloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (3,4-dichloro-2-methyl-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 416.

Example 616

4-(2-{[2-amino-6-(5-chloro-2-fluoro-3-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (5-chloro-2-fluoro-3-methyl-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 400.

Example 617

4-(2-{[2-amino-6-(3-chloro-2-fluorophenyl)pyrimidin-4-yl]amino}ethyl)benzamide

The title compound was prepared according to general procedure 2 from (3-chloro-2-fluoro-phenyl)boronic acid and Intermediate 45. LCMS $[M+H]^+$ 386.

Example 618

N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-2,2-dimethylpropanamide

The title compound was prepared according to general procedure 18 from Intermediate 47 and 2,2-dimethylpropanoyl chloride. LCMS $[M+H]^+$ 438.

Example 619

1-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-3-(propan-2-yl)urea

A mixture of Intermediate 47 and isopropyl isocyanate were stirred in DCM at 20 °C for 24 h. The desired compound precipitated and the solid was filtered off and washed with DCM. LCMS $[M+H]^+$ 439.

Example 620

tert-butyl N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]carbamate

The title compound was prepared according to general procedure 18 from Intermediate 47 and di-tert-butyl dicarbonate. LCMS $[M+H]^+$ 454.

Example 621

N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]cyclopropanecarboxamide

The title compound was prepared according to general procedure 18 from Intermediate 47 and cyclopropanecarbonyl chloride. LCMS $[M+H]^+$ 422.

Example 622

N-[3-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-2-methylpropane-1-sulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 47 and isobutylsulfonyl chloride. LCMS $[M+H]^+$ 474.

Example 623

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]propane-2-sulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and isopropylsulfonyl chloride. LCMS $[M+H]^+$ 460.

Example 624

N-[4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)phenyl]-2-methylpropane-1-sulfonamide

The title compound was prepared according to general procedure 18 from Intermediate 48 and isobutylsulfonyl chloride. LCMS $[M+H]^+$ 474.

Example 625

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzonitrile

4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (150 mg, 0,59 mmol), 4-(2-aminoethyl)benzonitrile hydrochloride (110 mg, 0,59 mmol), K_2CO_3 (240 mg, 1,8 mmol) and MeCN (5 mL) were heated (microwave reactor) for 1 hour at 170°C. ~400 mL was taken out, added some MeOH and purified by basic prep-HPLC to afford 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzonitrile. LCMS $[M+H]^+$ 364

Example 626

4-N-methyl-6-(2-phenylethynyl)pyrimidine-2,4-diamine

N_2 was flushed trough a mixture of 6-iodo-4-N-methylpyrimidine-2,4-diamine

(intermediate 17) (50 mg, 0,20 mmol), ethynylbenzene (100 mg, 1,0 mmol), K_2CO_3 (110 mg, 0,80 mmol), DME (0,75 mL) and water (0,75 mL). $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (33 mg, 0,040 mmol) and CuI (7,6 mg, 0,040 mmol) were added and the mixture was heated in a sealed tube at 90°C for 90 min. The organic phase was removed in vacuo. The crude material was dissolved in MeOH and purified by prep-HPLC, to afford 4-N-methyl-6-(2-phenylethynyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 225.

Example 627

3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzamide

Step 1. 3-(2-aminoethyl)benzamide was prepared according to general procedure 19 from 3-bromobenzamide.

Step 2. The title compound was prepared according to general procedure 9 from 3-(2-aminoethyl)benzamide and intermediate 24. LCMS $[M+H]^+$ 382.

Example 628

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-N-methyl-benzamide

Step 1. A mixture of 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzoic acid (from step 1 of the synthesis of intermediate 45, 1.0 equiv.), TBTU (1.2 equiv.), and DMF was stirred at 20 °C for 5 min. Then methyl amine (3.0 equiv.) was added and the resulting mixture was stirred at 20 °C for 16 h. The mixture was then diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried and purified by silica gel chromatography.

Step 2. The title compound was prepared according to general procedure 2 from the material from step 1 and (3-chloro-2-methyl-phenyl)boronic acid. LCMS $[M+H]^+$ 396.

Example 629

[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-pyrrolidin-1-yl-methanone

Step 1. A mixture of 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzoic acid (from step 1 of the synthesis of intermediate 45, 1.0 equiv.), TBTU (1.2 equiv.), and DMF was stirred at 20 °C for 5 min. Then pyrrolidine (3.0 equiv.) was added and the resulting mixture was stirred at 20 °C for 16 h. The mixture was

then diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried and purified by silica gel chromatography.

Step 2. The title compound was prepared according to general procedure 2 from the material from step 1 and (3-chloro-2-methyl-phenyl)boronic acid.

LCMS $[M+H]^+$ 436.

Example 630

7-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-4H-1,4-benzoxazin-3-one

Step 1. 7-(2-aminoethylamino)-4H-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 7-bromo-4H-1,4-benzoxazin-3-one.

Step 2. The title compound was prepared according to general procedure 9 from the material from step 1 and intermediate 24. LCMS $[M+H]^+$ 425. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.59 - 7.62 (m, 1 H), 7.30 - 7.39 (m, 2 H), 6.77 (d, *J*=8.5 Hz, 1 H), 6.56 (d, *J*=2.5 Hz, 1 H), 6.49 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.04 (s, 1 H), 4.52 (s, 2 H), 3.74 (t, *J*=6.2 Hz, 2 H), 3.45 (t, *J*=6.0 Hz, 2 H), 2.38 (s, 3 H).

Example 631

6-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-4-methyl-1,4-benzoxazin-3-one

Step 1. 6-(2-aminoethylamino)-4-methyl-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-4-methyl-1,4-benzoxazin-3-one.

Step 2. The title compound was prepared according to general procedure 9 from 6-(2-aminoethylamino)-4-methyl-1,4-benzoxazin-3-one and intermediate 24. $[M+H]^+$ 439. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.61 (dd, *J*=7.6, 1.3 Hz, 1 H), 7.30 - 7.39 (m, 2 H), 6.88 (d, *J*=8.5 Hz, 1 H), 6.63 (d, *J*=2.8 Hz, 1 H), 6.54 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.04 (s, 1 H), 4.52 (d, *J*=0.6 Hz, 2 H), 3.75 - 3.80 (m, 2 H), 3.49 (t, *J*=6.0 Hz, 2 H), 3.33 (s, 3 H), 2.37 (s, 3 H).

Example 632

7-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-3H-quinazolin-4-one

Step 1. 6-(2-aminoethylamino)-3H-quinazolin-4-one was prepared according to general procedure 13 from 7-bromo-3H-quinazolin-4-one.

Step 2. The title compound was prepared according to general procedure 9 from

6-(2-aminoethylamino)-3H-quinazolin-4-one and intermediate 24.
$[M+H]^+$ 422. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.08 - 8.10 (m, 1 H), 7.69 - 7.72 (m, 1 H), 7.59 - 7.63 (m, 1 H), 7.48 - 7.52 (m, 1 H), 7.32 - 7.40 (m, 1 H), 7.20 - 7.25 (m, 1 H), 6.04 (s, 1 H), 3.68 (dd, *J*=8.8, 5.7 Hz, 2 H), 3.49 - 3.54 (m, 2 H), 2.39 (s, 3 H).

Example 633
6-[2-[[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]ethylamino]-4-methyl-1,4-benzoxazin-3-one
Step 1. 6-(2-aminoethylamino)-4-methyl-1,4-benzoxazin-3-one was prepared according to general procedure 13 from 6-bromo-4-methyl-1,4-benzoxazin-3-one.
Step 2. The title compound was prepared according to general procedure 9 from 6-(2-aminoethylamino)-4-methyl-1,4-benzoxazin-3-one and intermediate 21.
$[M+H]^+$ 459. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.79 (dd, *J*=7.0, 2.8 Hz, 1 H), 7.47 - 7.53 (m, 2 H), 6.93 (d, *J*=8.8 Hz, 1 H), 6.77 (d, *J*=2.5 Hz, 1 H), 6.67 (dd, *J*=8.5, 2.5 Hz, 1 H), 6.15 (s, 1 H), 4.55 (s, 2 H), 3.77 - 3.83 (m, 2 H), 3.53 - 3.58 (m, 2 H), 3.34 (s, 3 H).

Example 634
6-(3-chloro-2-methylphenyl)-4-N-[2-(3-nitrophenyl)ethyl]pyrimidine-2,4-diamine
Step 1: A mixture of 2-amino-4,6-dichloropyrimidine (1.0 equiv.), 2-(3-nitrophenyl)ethylammonium chloride (1.3 equiv.), and diisopropylethylamine (2.5 equiv.) in 2-propanol was stirred at 100 °C in a sealed vial for 16 h. The reaction mixture was then diluted with $NaHCO_3$ (aq) and extracted with DCM. The crude material was then purified by silica gel chromatography.
Step 2: A mixture of the product from step 1 (1.0 equiv.), (3-chloro-2-methyl-phenyl)boronic acid (1.2 equiv.), K_2CO_3 (3.0 equiv.) and $Pd(PPh_3)_4$ (0.05 equiv.) in 1,4-dioxane and water was stirred at 90 °C for 16 h. Thereafter water was added and the mixture was extracted with DCM ×3. The combined organic phases were concentrated and purified by silica gel chromatography. LCMS [M+H]+ 384.

Example 635

4-[2-[[2-amino-6-(2-chloro-3-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide

The title compound was prepared according to general procedure 9 from 4-(2-aminoethyl)benzenesulfonamide and intermediate 37. LCMS $[M+H]^+$ 418. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.83 - 7.87 (m, 2 H), 7.51 - 7.55 (m, 1 H), 7.44 - 7.49 (m, 2 H), 7.36 - 7.41 (m, 1 H), 7.33 - 7.36 (m, 1 H), 6.06 (s, 1 H), 3.81 (t, *J*=7.3 Hz, 2 H), 3.05 (t, *J*=7.1 Hz, 2 H), 2.47 (s, 3 H).

Example 636

4-[2-[[2-amino-6-(2,3,5-trichlorophenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide

Step 1. A mixture of 4,6-dichloropyrimidin-2-amine (0.10 g, 0.64 mmol), (2,3,5-trichlorophenyl)boronic acid (0.12 g, 0.53 mmol), potassium carbonate (0.22 g, 1.60 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (0.031 g, 0.027 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 60°C for 4 h. The mixture was then diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were concentrated and purified by silica gel chromatography. LCMS $[M+H]^+$ 308.

Step 2. The title compound was prepared according to general procedure 9 from 4-(2-aminoethyl)benzenesulfonamide and the material from step 1. LCMS $[M+H]^+$ 472. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.89 - 7.90 (m, 1 H), 7.85 (d, *J*=8.5 Hz, 2 H), 7.61 - 7.62 (m, 1 H), 7.46 (d, *J*=8.5 Hz, 2 H), 6.11 (s, 1 H), 3.82 (s, 2 H), 3.05 (s, 2 H).

Example 637

4-[2-[[2-amino-6-(2,3,4-trichlorophenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide

The title compound was prepared according to general procedure 9 from 4-(2-aminoethyl)benzenesulfonamide and intermediate 26. LCMS $[M+H]^+$ 472. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.82 - 7.87 (m, 2 H), 7.71 (d, *J*=8.5 Hz, 1 H), 7.44 - 7.50 (m, 3 H), 6.10 (s, 1 H), 3.81 (t, *J*=7.1 Hz, 2 H), 3.05 (t, *J*=7.1 Hz, 2 H).

Example 638

4-[2-[[2-amino-6-(2,4-dichloro-3-methoxy-phenyl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide

Step 1. A mixture of 4,6-dichloropyrimidin-2-amine (0.10 g, 0.64 mmol), (2,4-dichloro-3-methoxy-phenyl)boronic acid (0.12 g, 0.53 mmol), potassium carbonate (0.22 g, 1.60 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (0.031 g, 0.027 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 60°C for 4 h. The mixture was then diluted with $NaHCO_3$ and extracted with DCM ×3. The combined organics were concentrated and purified by silica gel chromatography. LCMS $[M+H]^+$ 304.

Step 2. The title compound was prepared according to general procedure 9 from 4-(2-aminoethyl)benzenesulfonamide and the material from step 1. LCMS $[M+H]^+$ 468. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.83 - 7.87 (m, 2 H), 7.57 (d, *J*=8.5 Hz, 1 H), 7.46 (d, *J*=8.5 Hz, 2 H), 7.29 (d, *J*=8.5 Hz, 1 H), 6.09 (s, 1 H), 3.92 - 3.94 (m, 3 H), 3.81 (t, *J*=7.3 Hz, 2 H), 3.05 (t, *J*=7.1 Hz, 2 H).

Example 639

6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-methyl-5-nitro-imidazol-1-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(2-methyl-5-nitro-imidazol-3-ium-1-yl)ethylammonium dichloride and intermediate 24. $[M+H]^+$ 388. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.98 (br. s., 1 H), 7.61 (dd, *J*=7.9, 1.6 Hz, 1 H), 7.33 - 7.39 (m, 1 H), 7.29 - 7.33 (m, 1 H), 5.98 (s, 1 H), 4.65 - 4.70 (m, 2 H), 3.97 (t, *J*=5.8 Hz, 2 H), 2.53 (s, 3 H), 2.36 (s, 3 H).

Example 640

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(2-methyl-1,3-benzothiazol-6-yl)amino]ethyl]pyrimidine-2,4-diamine

Step 1. N'-(2-methyl-1,3-benzothiazol-6-yl)ethane-1,2-diamine was prepared according to general procedure 13 from 6-iodo-2-methyl-1,3-benzothiazole.

Step 2. The title compound was prepared according to general procedure 9 from intermediate 24 and N'-(2-methyl-1,3-benzothiazol-6-yl)ethane-1,2-diamine. $[M+H]^+$ 425. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.86 (d, *J*=8.8 Hz, 1 H), 7.74 (br. s., 1 H), 7.41 - 7.49 (m, 2 H), 7.18 (dd, *J*=8.8, 2.2 Hz, 1 H), 7.04 -

7.13 (m, 2 H), 5.91 (s, 1 H), 3.86 - 3.93 (m, 2 H), 3.52 - 3.58 (m, 2 H), 2.89 (s, 3 H), 2.25 (s, 3 H).

Example 641

4-[2-[[2-amino-6-(benzothiophen-3-yl)pyrimidin-4-yl]amino]ethyl]benzenesulfonamide

The title compound was prepared according to general procedure 2 from intermediate 25 and benzothiophen-3-ylboronic acid. $[M+H]^+$ 426. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.16 (s, 1 H), 8.02 - 8.06 (m, 1 H), 7.96 - 8.00 (m, 1 H), 7.83 - 7.88 (m, 2 H), 7.45 - 7.57 (m, 4 H), 6.34 (s, 1 H), 3.84 (t, *J*=7.1 Hz, 2 H), 3.07 (t, *J*=7.1 Hz, 2 H).

Example 642

N4-[2-(4-aminophenyl)ethyl]-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine

Step 1. A mixture of 4-(2-aminoethyl)aniline (1 equiv.), 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (1 equiv.), and Hünigs base (1.1 equiv.) in 2-propanol was stirred at 110 °C for 4 h. The mixture was then cooled, poured into saturated $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried with $MgSO_4$ and concentrated. The crude material was suspended in hot MeOH and filtered. Evaporation of the solvent afforded N4-[2-(4-aminophenyl)ethyl]-6-chloro-pyrimidine-2,4-diamine. $[M+H]^+$ 264.

Step 2. The title compound was produced according to general procedure 9 from the material in step 1 and (3-chloro-2-methyl-phenyl)boronic acid. $[M+H]^+$ 354.

Example 643

4-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propylamino]benzamide

Step 1. 4-(3-aminopropylamino)benzamide was prepared according to general procedure 13 from 4-iodobenzamide and propane-1,3-diamine.

Step 2. The title compound was produced according to general procedure 9 from 4-(3-aminopropylamino)benzamide and intermediate 24. $[M+H]^+$ 411. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.63 - 7.69 (m, 2 H), 7.40 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.13 - 7.24 (m, 2 H), 6.62 (d, *J*=8.8 Hz, 2 H), 5.82 (s, 1 H), 3.48 (br. s., 2 H), 3.24 (t, *J*=6.6 Hz, 2 H), 2.31 (s, 3 H), 1.92 (t, *J*=6.8 Hz, 2 H).

Example 644

4-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propylamino]-N-methyl-benzenesulfonamide

Step 1. 4-(3-aminopropylamino)-N-methyl-benzenesulfonamide was prepared according to general procedure 13 from 4-iodo-N-methyl-benzenesulfonamide and propane-1,3-diamine.

Step 2. The title compound was produced according to general procedure 9 from 4-(3-aminopropylamino)-N-methyl-benzenesulfonamide and intermediate 24. $[M+H]^+$ 461. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.51 - 7.56 (m, 2 H), 7.38 - 7.43 (m, 1 H), 7.15 - 7.24 (m, 2 H), 6.68 (d, *J*=8.8 Hz, 2 H), 5.82 (s, 1 H), 3.48 (br. s., 2 H), 3.25 (t, *J*=6.8 Hz, 2 H), 2.46 (s, 3 H), 2.32 (s, 3 H), 1.92 (quin, *J*=6.9 Hz, 2 H).

Example 645

6-(3-chloro-2-methyl-phenyl)-N4-[3-[(2-methyl-1,3-benzothiazol-6-yl)amino]propyl]pyrimidine-2,4-diamine

Step 1. N'-(2-methyl-1,3-benzothiazol-6-yl)propane-1,3-diamine was prepared according to general procedure 13 from 6-iodo-2-methyl-1,3-benzothiazole and propane-1,3-diamine.

Step 2. The title compound was produced according to general procedure 9 from N'-(2-methyl-1,3-benzothiazol-6-yl)propane-1,3-diamine and intermediate 24. $[M+H]^+$ 439. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.83 (d, *J*=8.8 Hz, 1 H), 7.58 - 7.63 (m, 2 H), 7.30 - 7.39 (m, 2 H), 7.26 (dd, *J*=8.8, 2.5 Hz, 1 H), 6.04 (s, 1 H), 3.67 (t, *J*=6.8 Hz, 2 H), 3.40 - 3.46 (m, 2 H), 2.84 (s, 3 H), 2.37 (s, 3 H), 2.07 (quin, *J*=7.1 Hz, 2 H).

Example 646

2-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]pyrimidine-4-carboxamide

The title compound was produced according to general procedure 12 from intermediate 58 and 2-chloropyrimidine-4-carboxamide. LCMS $[M+H]^+$ 399. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.49 (d, *J*=5.4 Hz, 1 H), 7.60 (dd, *J*=8.1, 1.4 Hz, 1 H), 7.28 - 7.39 (m, 2 H), 7.18 - 7.22 (m, 1 H), 5.97 (s, 1 H), 3.77 (s, 4 H), 2.35 (s, 3 H).

Example 647

The title compound was produced according to general procedure 12 from intermediate 58 and 6-chloropyridine-3-carboxamide. LCMS $[M+H]^+$ 398. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.48 (d, *J*=1.9 Hz, 1 H), 8.23 (d, *J*=9.2 Hz, 1 H), 7.61 (dd, *J*=7.6, 1.6 Hz, 1 H), 7.30 - 7.40 (m, 2 H), 7.01 (d, *J*=9.5 Hz, 1 H), 6.06 (s, 1 H), 3.80 - 3.87 (m, 2 H), 3.70 - 3.78 (m, 2 H), 2.37 (s, 3 H).

Example 648

1-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-ethyl-urea

The title compound was produced according to general procedure 21 from intermediate 47 and ethyl isocyanate. LCMS $[M+H]^+$ 425. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.40 (dd, *J*=7.4, 1.7 Hz, 1 H), 7.32 (s, 1 H), 7.14 - 7.24 (m, 4 H), 6.88 (d, *J*=6.6 Hz, 1 H), 5.78 (s, 1 H), 3.59 (br. s., 2 H), 3.22 (q, *J*=7.3 Hz, 2 H), 2.85 (t, *J*=7.3 Hz, 2 H), 2.32 (s, 3 H), 1.12 - 1.17 (m, 3 H).

Example 649

1-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-3-tert-butyl-urea

The title compound was produced according to general procedure 21 from intermediate 47 and tert-butyl isocyanate. LCMS $[M+H]^+$ 453. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.56 - 7.62 (m, 1 H), 7.45 (t, *J*=1.7 Hz, 1 H), 7.32 - 7.36 (m, 2 H), 7.14 - 7.19 (m, 1 H), 6.99 (ddd, *J*=8.1, 2.2, 1.1 Hz, 1 H), 6.87 (dq, *J*=7.6, 0.8 Hz, 1 H), 6.01 (s, 1 H), 3.77 (s, 2 H), 2.90 (s, 2 H), 2.37 (s, 3 H), 1.34 - 1.37 (m, 9 H).

Example 650

N-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]morpholine-4-carboxamide

A mixture of N4-[2-(3-aminophenyl)ethyl]-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 47) (1 equiv.), morpholine-4-carbonyl chloride (1.4 equiv.), and diisopropylethylamine (1.6 equiv.) in DCM was stirred at reflux for 16 h. The reaction mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 467. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 - 7.62 (m, 1 H), 7.41

(t, *J*=1.7 Hz, 1 H), 7.33 - 7.36 (m, 2 H), 7.19 - 7.24 (m, 1 H), 7.11 - 7.14 (m, 1 H), 6.94 - 6.98 (m, 1 H), 6.00 (s, 1 H), 3.78 (t, *J*=7.1 Hz, 2 H), 3.68 - 3.73 (m, 4 H), 3.48 - 3.53 (m, 4 H), 2.92 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H).

Example 651

3-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]-1,1-dimethyl-urea

A mixture of N4-[2-(3-aminophenyl)ethyl]-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 47) (1 equiv.), N,N-dimethylcarbamoyl chloride (1.3 equiv.), and diisopropylethylamine (1.6 equiv.) was stirred at 150 °C for 10 min. The reaction mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 425. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 - 7.62 (m, 1 H), 7.41 (t, *J*=1.7 Hz, 1 H), 7.33 - 7.36 (m, 2 H), 7.18 - 7.24 (m, 1 H), 7.11 - 7.15 (m, 1 H), 6.92 - 6.96 (m, 1 H), 6.01 (s, 1 H), 3.78 (t, *J*=7.1 Hz, 2 H), 3.01 - 3.03 (m, 6 H), 2.89 - 2.94 (m, 2 H), 2.37 (s, 3 H).

Example 652

N-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]pyrrolidine-1-carboxamide

A mixture of N4-[2-(3-aminophenyl)ethyl]-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 47) (1 equiv.), pyrrolidine-1-carbonyl chloride (1.3 equiv.), and diisopropylethylamine (1.6 equiv.) was stirred at 150 °C for 10 min. The reaction mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 451. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 - 7.61 (m, 1 H), 7.46 (t, *J*=1.6 Hz, 1 H), 7.33 - 7.36 (m, 2 H), 7.17 - 7.23 (m, 2 H), 6.94 (dt, *J*=7.1, 1.7 Hz, 2 H), 6.01 (s, 1 H), 3.78 (t, *J*=7.1 Hz, 2 H), 3.43 - 3.48 (m, 4 H), 2.92 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H), 1.95 - 2.00 (m, 4 H).

Example 653

isopropyl N-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was produced according to general procedure 18 from intermediate 47 and isopropyl carbonochloridate. LCMS $[M+H]^+$ 440. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.60 (dd, *J*=6.3, 2.8 Hz, 1 H), 7.47 (s, 1 H), 7.33 - 7.36 (m, 2 H), 7.17 - 7.23 (m, 2 H), 6.92 - 6.96 (m, 1 H), 6.00 (s, 1 H), 4.91

- 4.98 (m, 1 H), 3.77 (t, *J*=7.1 Hz, 2 H), 2.92 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H), 1.27 - 1.31 (m, 6 H).

Example 654

isobutyl N-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was produced according to general procedure 18 from intermediate 47 and isobutyl carbonochloridate. LCMS $[M+H]^+$ 454. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.58 - 7.61 (m, 1 H), 7.48 (s, 1 H), 7.33 - 7.35 (m, 2 H), 7.18 - 7.24 (m, 2 H), 6.92 - 6.97 (m, 1 H), 6.00 (s, 1 H), 3.90 (d, *J*=6.6 Hz, 2 H), 3.77 (t, *J*=7.1 Hz, 2 H), 2.93 (t, *J*=7.1 Hz, 2 H), 2.37 (s, 3 H), 1.91 - 2.03 (m, 1 H), 0.96 - 1.01 (m, 6 H).

Example 655

2,2-dimethylpropyl N-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]carbamate

The title compound was produced according to general procedure 18 from intermediate 47 and 2,2-dimethylpropyl carbonochloridate. LCMS $[M+H]^+$ 468. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.57 - 7.61 (m, 1 H), 7.49 (br. s., 1 H), 7.33 - 7.35 (m, 2 H), 7.19 - 7.24 (m, 2 H), 6.95 (dt, *J*=6.2, 1.9 Hz, 1 H), 6.00 (s, 1 H), 3.83 (s, 2 H), 3.77 (s, 2 H), 2.93 (s, 2 H), 2.37 (s, 3 H), 0.97 - 1.01 (m, 9 H).

Example 656

1-[6-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-3-pyridyl]-3-tert-butyl-urea

Step 1. A mixture of intermediate 24 (1 equiv.), N-(2-aminoethyl)-5-nitropyridin-2-amine, (1.3 equiv.), and Hünig's base (1.5 equiv.) was stirred in 2-propanol at 120 °C for 16 h. The mixture was then poured into water and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was used in step 2 without further purification.

Step 2. The crude material from step 1 (1 equiv.) was dissolved in EtOH, then $SnCl_2$ (5 equiv.) was added and the resulting mixture was stirred at reflux for 5 h. The mixture was then cooled and basified by addition of NaOH (5 M). The mixture was then extracted with DCM ×3. The combined organics were dried

($MgSO_4$) and concentrated. The crude material was used in step 3 without further purification.

Step 3. A mixture of the crude material from step 2 (1 equiv.) and tert-butyl isocyanate (3 equiv.) in DCM was stirred at reflux for 16 h. The mixture was then concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 469. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.18 (dd, *J*=2.5, 0.6 Hz, 1 H), 7.77 (dd, *J*=9.5, 2.5 Hz, 1 H), 7.60 (dd, *J*=7.7, 2.1 Hz, 1 H), 7.30 - 7.38 (m, 2 H), 7.07 (dd, *J*=9.6, 0.8 Hz, 1 H), 6.07 (s, 1 H), 3.82 (s, 2 H), 3.66 (s, 2 H), 2.36 (s, 3 H), 1.36 (s, 9 H).

Example 657

tert-butyl N-[6-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-3-pyridyl]carbamate

Step 1. A mixture of intermediate 24 (1 equiv.), N-(2-aminoethyl)-5-nitropyridin-2-amine, (1.3 equiv.), and Hünig's base (1.5 equiv.) was stirred in 2-propanol at 120 °C for 16 h. The mixture was then poured into water and extracted with DCM ×3. The combined organics were dried (MgSO4) and concentrated. The crude material was used in step 2 without further purification.

Step 2. The crude material from step 1 (1 equiv.) was dissolved in EtOH, then $SnCl_2$ (5 equiv.) was added and the resulting mixture was stirred at reflux for 5 h. The mixture was then cooled and basified by addition of NaOH (5 M). The mixture was then extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was used in step 3 without further purification.

Step 3. A mixture of the crude material from step 2 and di-tert-butyl dicarbonate in DCM was stirred at reflux for 16 h. The mixture was then concentrated and purified by prep-LC. LCMS $[M+H]^+$ 470. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.23 (br. s., 1 H), 7.84 (dd, *J*=9.5, 2.5 Hz, 1 H), 7.58 - 7.62 (m, 1 H), 7.28 - 7.38 (m, 2 H), 7.09 (dd, *J*=9.8, 0.6 Hz, 1 H), 6.07 (s, 1 H), 3.80 - 3.86 (m, 2 H), 3.64 - 3.70 (m, 2 H), 2.36 (s, 3 H), 1.51 (s, 9 H).

Example 658

N2-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-1,3,5-triazine-2,4,6-triamine

The title compound was produced according to general procedure 12 from intermediate 58 and 6-chloro-1,3,5-triazine-2,4-diamine. LCMS $[M+H]^+$ 387.

Example 659

2-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-4-(trifluoromethyl)pyrimidine-5-carboxamide

The title compound was produced according to general procedure 12 from intermediate 58 and 2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxamide. LCMS $[M+H]^+$ 467. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.50 - 8.62 (m, 1 H), 7.57 - 7.61 (m, 1 H), 7.29 - 7.38 (m, 2 H), 5.99 (d, *J*=7.3 Hz, 1 H), 3.76 (br. s., 4 H), 2.37 (s, 3 H).

Example 660

N-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-3-fluoro-benzenesulfonamide

A mixture of N4-(2-aminoethyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 58) (1 equiv.), 3-fluorobenzenesulfonyl chloride (1.3 equiv.), and Hünig's base (2.1 equiv.) in DCM was stirred 18 h at 20 °C. The reaction mixture was concentrated and purified by prep-LC. LCMS $[M+H]^+$ 436. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.67 - 7.71 (m, 1 H), 7.56 - 7.63 (m, 3 H), 7.32 - 7.42 (m, 3 H), 6.04 (s, 1 H), 3.61 (t, *J*=6.0 Hz, 2 H), 3.16 (t, *J*=6.0 Hz, 2 H), 2.38 (s, 3 H).

Example 661

2-(2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)-1-(4-(methylsulfonyl)phenyl)ethanol

Step 1: 2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone

To the solution of 1-(4-(methylsulfonyl)phenyl)ethan-1-one (5.00 g, 25.2 mmol) in $CHCl_3$ (100 mL) was added Br_2 (4.0 0 g, 25.2 mmol) in $CHCl_3$ (15 mL) dropwise over period of 1 h, the mixture was stirred for 1 h at RT (15 °C). The solution was washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude product was recrystallized from EtOH (50 mL) at RT to afford a white solid as product **20** (4.60 g, 16.6 mmol, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.12 (s, 3 H), 4.48 (s, 2 H), 8.10 (m, 2 H), 8.18 (m, 2 H) ppm.

Step 2: To the solution of 2-Bromo-1-(4-(methylsulfonyl)phenyl)ethanone (5.30 g, 19.1 mmol) in MeCN (53 mL) was added hexamethylenetetramine (2.70 g, 19.3

mmol), the mixture was stirred for 2 h. at R.T. The product was isolated by filtration and dried under high vacuum (7.20 g), and used for next step without further purification.

Step 3: 2-Amino-1-(4-(methylsulfonyl)phenyl)ethanone hydrochloride

To the solution of concentrated HCl (10 mL) in EtOH (40 mL) was added 2-amino-1-(4-(methylsulfonyl)phenyl)ethanone (7.2 g, 17.3 mmol) at RT. The mixture was stirred for 2 h at 50 °C. After cooling to 5 °C, the resulting white solid was collected by filtration, washed with EtOH (10 mL). The solid was dissolved in the mixture of H_2O (12 mL) and concentrated HCl (0.5 mL) at 70 °C, the hot solution was filtered and the filtrate was cooled to 5 °C, the crystalline white solid was isolated by filtration, washed with ice-cold H_2O (5 mL) and EtOH (5 mL), dried under high vacuum to afford the product (2.30 g, 9.2 mmol, 53 %). ^{1}H NMR (400 MHz, D_2O): δ = 3.17 (d, *J* = 2.8 Hz, 2 H), 4.64 (s, 3 H), 7.99 (m, 2 H), 8.09 (m, 2 H) ppm.

Step 4: 2-amino-1-(4-(methylsulfonyl)phenyl)ethan-1-ol

At 0 °C, $NaBH_4$ (0.30 g, 8.0 mmol) was dissolved in MeOH (30 mL), KOH (0.22g, 3.9 mmol) in MeOH (4 mL) was added carefully, then 2-Amino-1-(4-(methylsulfonyl)phenyl)ethanone hydrochloride (1.00 g, 4.0 mmol) was added in small portions. The mixture was stirred for 30 min at 0 °C and 30 min at RT. After removal of solvent under reduced pressure, the residue was treated with saturated $NaHCO_3$ (10 mL). After extraction with DCM (20 mL x 4), the combined organic layers was washed with brine (5 mL), dried over Na_2SO_4. Removal of solvent under reduced pressure, gave the product (0.25 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (m, 1 H), 3.07 (s, 3 H), 3.12 (m, 1 H), 4.73 (m, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 8.4 Hz, 2 H) ppm.

Step 5: 2-(2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)-1-(4-(methylsulfonyl)phenyl)ethanol

A mixture of 2-amino-1-(4-(methylsulfonyl)phenyl)ethan-1-ol (190 mg, 0.88 mmol), intermediate 24 (266 mg, 1.05 mmol) and triethylamine (0.19 mL, 1.32 mmol) in isopropanol (5 mL) was stirred overnight at 95 °C. After cooling to RT and removal of solvent under reduced pressure, the residue was purified by preparative HPLC to yield the product (65 mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.08 (s, 3 H), 3.20 (s, 3 H), 3.61 (br, 1 H), 4.90 (s, 1 H), 5.81 (s, 1 H), 5.84 (m, 1H), 6.11 (s, 2 H), 7.20 (m, 3 H), 7.26 (m, 1 H), 7.70 (m, 2 H), 7.90 (m, 2 H) ppm.

Example 662

N-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]morpholine-4-carboxamide

A mixture of N4-(2-aminoethyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 58) (1 equiv.), morpholine-4-carbonyl chloride (1.4 equiv.), and Hünig's base (2.1 equiv.) in DCM was stirred 18 h at 20 °C. The reaction mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 391. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.61 (dd, *J*=7.1, 2.1 Hz, 1 H), 7.31 - 7.40 (m, 2 H), 6.04 (d, *J*=0.9 Hz, 1 H), 3.62 - 3.66 (m, 6 H), 3.40 - 3.44 (m, 2 H), 3.33 - 3.37 (m, 4 H), 2.38 (s, 3 H).

Example 663

1-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-3-(3-fluorophenyl)urea

A mixture of N4-(2-aminoethyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (intermediate 58) (1 equiv.) and 3-fluorophenyl isocyanate (1.4 equiv.) in DCM was stirred 18 h at 20 °C. The reaction mixture was concentrated and purified by preparative LC. LCMS $[M+H]^+$ 415. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.60 (dd, *J*=7.9, 1.3 Hz, 1 H), 7.29 - 7.38 (m, 3 H), 7.20 - 7.26 (m, 1 H), 7.00 (ddd, *J*=8.2, 2.1, 0.8 Hz, 1 H), 6.66 - 6.72 (m, 1 H), 6.04 (s, 1 H), 3.63 - 3.68 (m, 2 H), 3.45 - 3.49 (m, 2 H), 2.37 (s, 3 H).

Example 664

6-(3-chloro-2-methyl-phenyl)-N4-[2-(4-isopropylsulfonylanilino)ethyl]pyrimidine-2,4-diamine

Step 1. N'-(4-isopropylsulfonylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-4-isopropylsulfonyl-benzene and ethylenediamine.

Step 2. The title compound was prepared according to general procedure 9 from the crude material of step 1 and intermediate 24. $[M+H]^+$ 460. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.51 - 7.62 (m, 3 H), 7.29 - 7.39 (m, 2 H), 6.74 - 6.79 (m, 2 H), 6.01 (s, 1 H), 3.76 (t, *J*=6.2 Hz, 2 H), 3.51 (t, *J*=6.2 Hz, 2 H), 3.13 - 3.22 (m, 1 H), 2.37 (s, 3 H), 1.22 (d, *J*=7.0 Hz, 6 H).

Example 665

6-(3-chloro-2-methyl-phenyl)-N4-[2-(4-methylsulfinylanilino)ethyl]pyrimidine-2,4-diamine

Step 1. N'-(4-methylsulfinylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-4-methylsulfinyl-benzene and ethylenediamine.

Step 2. The title compound was prepared according to general procedure 9 from the crude material of step 1 and intermediate 24. LCMS $[M+H]^+$ 416.

Example 666

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-3-fluoro-benzamide

Step 1. 4-(2-aminoethyl)-3-fluoro-benzamide was prepared according to general procedure 22 from 4-bromo-3-fluoro-benzamide.

Step 2. The title compound was prepared according to general procedure 9 from the material from step 1 and intermediate 24. [M+H]+ 400.

Example 667

6-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]azetidin-1-yl]pyridine-3-sulfonamide

Step 1. A mixture of 4-fluorobenzenesulfonamide (1 equiv.), tert-butyl N-(azetidin-3-yl)carbamate (1.3 equiv.), and diisopropylethylamine (1.3 equiv.) was stirred in acetonitrile at 150 °C for 1 h in a sealed vial. The reaction mixture was then concentrated and purified by silica gel chromatography using MeOH (0 – 9%) in DCM.

Step 2. Tert-butyl N-[1-(4-sulfamoylphenyl)azetidin-3-yl]carbamate from step 1 was stirred in TFA at 20 °C for 2 h. The reaction mixture was then concentrated and used without further purification in step 3.

Step 3. The title compound was prepared according to general procedure 9 from the material from step 2 and intermediate 24. LCMS $[M+H]^+$ 445.

Example 668

tert-butyl N-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propyl]carbamate

Step 1. A mixture of tert-butyl N-(3-aminopropyl)carbamate (1.25 equiv.), 4,6-dichloropyrimidin-2-amine (1 equiv.), and Hünig's base (1.5 equiv.) in 2-propanol

was stirred at 100 °C for 16 h. The reaction mixture was then poured into water and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude material was purified by silica gel chromatography which afforded tert-butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate
Step 2. The title compound was prepared according to general procedure 2 from tert-butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate (prepared in step 1) and (3-chloro-2-methyl-phenyl)boronic acid. LCMS $[M+H]^+$ 392. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.57 - 7.63 (m, 1 H), 7.31 - 7.40 (m, 2 H), 6.04 (s, 1 H), 3.55 (t, J=6.8 Hz, 2 H), 3.14 (t, J=7.0 Hz, 2 H), 2.39 (s, 3 H), 1.81 (t, J=7.0 Hz, 2 H), 1.44 (s, 9 H).

Example 669
4-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propylamino]benzenesulfonamide
Step 1. 4-(3-aminopropylamino)benzenesulfonamide was prepared according to general procedure 13 from 4-iodobenzenesulfonamide and propane-1,3-diamine.
Step 2. The title compound was prepared according to general procedure 9 from 4-(3-aminopropylamino)benzenesulfonamide and intermediate 24. LCMS $[M+H]^+$ 447.

Example 670
4-[[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]-2,2-dimethyl-propyl]amino]benzenesulfonamide
Step 1. A mixture of 4-bromobenzenesulfonamide (1 equiv.), CuCl (0.1 equiv.), and KOH (2 equiv.) were stirred in 2,2-dimethylpropane-1,3-diamine (5 equiv.) at 40 °C for 72 h. the reaction mixture was extracted with hot EtOAc and concentrated. The crude 4-[(3-amino-2,2-dimethyl-propyl)amino]benzenesulfonamide was then washed with diethyl ether and used in step 2.
Step 2. The title compound was prepared according to general procedure 9 from 4-[(3-amino-2,2-dimethyl-propyl)amino]benzenesulfonamide and intermediate 24. LCMS $[M+H]^+$ 475.

Example 671
6-(3-chloro-2-methyl-phenyl)-N4-[2,2-dimethyl-3-[(2-methyl-1,3-benzothiazol-6-

yl)amino]propyl]pyrimidine-2,4-diamine

Step 1. A mixture of 6-iodo-2-methyl-1,3-benzothiazole (1 equiv.), CuCl (0.1 equiv.), and KOH (2 equiv.) were stirred in 2,2-dimethylpropane-1,3-diamine (5 equiv.) at 40 °C for 72 h. the reaction mixture was extracted with hot EtOAc and concentrated. The crude residue was then purified by preparative LC to afford 2,2-dimethyl-N'-(2-methyl-1,3-benzothiazol-6-yl)propane-1,3-diamine. $[M+H]^+$ 250.

Step 2. The title compound was prepared according to general procedure 9 from 2,2-dimethyl-N'-(2-methyl-1,3-benzothiazol-6-yl)propane-1,3-diamine and intermediate 24. LCMS $[M+H]^+$ 467. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.56 - 7.61 (m, 2 H), 7.31 - 7.37 (m, 1 H), 7.25 - 7.30 (m, 1 H), 7.12 (d, J=2.2 Hz, 1 H), 6.92 - 6.97 (m, 1 H), 6.09 (s, 1 H), 3.59 (s, 2 H), 3.08 (s, 2 H), 2.75 (s, 3 H), 2.32 (s, 3 H), 1.11 (s, 6 H).

Example 672

6-(3-Chloro-2-methyl-phenyl)-N4-[2-(3-isopropylsulfonylanilino)ethyl]pyrimidine-2,4-diamine

Step 1. N'-(3-isopropylsulfonylphenyl)ethane-1,2-diamine was prepared according to general procedure 13 from 1-bromo-3-isopropylsulfonyl-benzene and ethylenediamine.

Step 2. The title compound was prepared according to general procedure 9 from N'-(3-isopropylsulfonylphenyl)ethane-1,2-diamine and 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (intermediate 24). LCMS $[M+H]^+$ 460. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.59 - 7.62 (m, 1 H), 7.35 (s, 3 H), 7.22 - 7.25 (m, 1 H), 7.05 - 7.09 (m, 1 H), 6.94 - 6.98 (m, 1 H), 6.01 (s, 1 H), 3.65 - 3.70 (m, 2 H), 3.45 - 3.50 (m, 2 H), 2.38 (s, 3 H), 1.26 (d, *J*=7.0 Hz, 6 H).

Example 673

6-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]propylamino]pyridine-3-carboxamide

The title compound was prepared according to general procedure 12 from 6-chloropyridine-3-carboxamide and intermediate 59. LCMS $[M+H]^+$ 412.

Example 674

2-[3-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-

yl]amino]propylamino]pyrimidine-4-carboxamide

The title compound was prepared according to general procedure 12 from 2-chloropyrimidine-4-carboxamide and intermediate 59. LCMS [M+H]+ 413.

Example 675

6-(3-chloro-2-methyl-phenyl)-N4-[2-(4-isopropylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine

Step 1. 2-(4-isopropylsulfonylphenyl)ethanamine was was prepared according to general procedure 22 from 1-bromo-4-isopropylsulfonyl-benzene.

Step 2. The title compound was prepared according to general procedure 9 from 2-(4-isopropylsulfonylphenyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 445.

Example 676

Step 1. 2-(3-isopropylsulfonylphenyl)ethanamine was was prepared according to general procedure 22 from 1-bromo-3-isopropylsulfonyl-benzene.

Step 2. The title compound was prepared according to general procedure 9 from 2-(3-isopropylsulfonylphenyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 445. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.73 - 7.80 (m, 2 H), 7.67 (s, 1 H), 7.60 (t, J=7.4 Hz, 2 H), 7.31 - 7.38 (m, 2 H), 5.98 (d, J=1.6 Hz, 1 H), 3.85 (t, J=7.0 Hz, 2 H), 3.34 (obstructed by solvent signal, m, 1 H), 3.10 (t, J=7.0 Hz, 2 H), 2.36 (s, 3 H), 1.24 (d, J=7.0 Hz, 6 H).

Example 677

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-2-fluoro-benzamide

Step 1. 4-(2-aminoethyl)-2-fluoro-benzamide was prepared according to general procedure 22 from 4-bromo-2-fluoro-benzamide.

Step 2. The title compound was prepared according to general procedure 9 from 4-(2-aminoethyl)-2-fluoro-benzamide and intermediate 24. LCMS $[M+H]^+$ 400. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.79 (t, J=7.9 Hz, 1 H), 7.58 - 7.62 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.22 (dd, J=7.9, 1.6 Hz, 1 H), 7.18 (dd, J=12.2, 1.4 Hz, 1 H), 6.00 (s, 1 H), 3.82 (t, J=7.1 Hz, 2 H), 3.03 (t, J=7.1 Hz, 2 H), 2.37 (s, 3 H).

Example 678

6-(3-chloro-2-methyl-phenyl)-N4-[2-(3-fluoro-4-methylsulfonyl-

phenyl)ethyl]pyrimidine-2,4-diamine

Step 1. 2-(3-fluoro-4-methylsulfonyl-phenyl)ethylamine was prepared according to general procedure 22 from 4-bromo-2-fluoro-1-methylsulfonyl-benzene.

Step 2. The title compound was prepared according to general procedure 9 from 2-(3-fluoro-4-methylsulfonyl-phenyl)ethylamine and intermediate 24. LCMS $[M+H]^+$ 435. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.86 (t, J=7.7 Hz, 1 H), 7.58 - 7.62 (m, 1 H), 7.31 - 7.38 (m, 4 H), 6.00 (s, 1 H), 3.84 (t, J=7.0 Hz, 2 H), 3.22 - 3.24 (m, 3 H), 3.08 (t, J=7.0 Hz, 2 H), 2.37 (s, 3 H).

Example 679

5-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]-2-hydroxy-benzamide

Step 1. 2-(3-carbamoyl-4-hydroxy-phenyl)ethylamine was prepared according to general procedure 22 from 6-bromo-2,2-dimethyl-3H-1,3-benzoxazin-4-one.

Step 2. The title compound was prepared according to general procedure 9 from 2-(3-carbamoyl-4-hydroxy-phenyl)ethylamine and intermediate 24. LCMS $[M+H]^+$ 398.

Example 680

6-(3-chloro-2-methyl-phenyl)-N4-(4-phenylbutyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 4-phenylbutan-1-amine and intermediate 24. LCMS $[M+H]^+$ 367. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.57 - 7.61 (m, 1 H), 7.33 - 7.36 (m, 2 H), 7.23 - 7.28 (m, 2 H), 7.12 - 7.21 (m, 3 H), 6.01 (s, 1 H), 3.54 (t, J=6.8 Hz, 2 H), 2.65 - 2.70 (m, 2 H), 2.38 (s, 3 H), 1.62 - 1.77 (m, 4 H).

Example 681

6-(3-chloro-2-methyl-phenyl)-N4-[2-(cyclohexen-1-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(cyclohexen-1-yl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 343. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.62 (m, 1 H), 7.31 - 7.39 (m, 2 H), 6.03 (s, 1 H), 5.46 - 5.52 (m, 1 H), 3.62 (t, J=7.1 Hz, 2 H), 2.38 (s, 3 H), 2.26 (t, J=6.6 Hz, 2 H), 1.95 - 2.07 (m, 4 H), 1.62 - 1.70 (m, 2 H), 1.53 - 1.61 (m, 2 H).

Example 682

N4-but-3-enyl-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine
The title compound was prepared according to general procedure 9 from but-3-en-1-amine and intermediate 24. LCMS $[M+H]^+$ 289. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.62 (m, 1 H), 7.32 - 7.38 (m, 2 H), 6.03 (s, 1 H), 5.87 (ddt, J=17.1, 10.3, 6.7, 6.7 Hz, 1 H), 5.14 (dq, J=17.1, 1.7 Hz, 1 H), 5.09 (ddt, J=10.2, 2.0, 1.1, 1.1 Hz, 1 H), 3.60 (t, J=7.0 Hz, 2 H), 2.39 - 2.44 (m, 2 H), 2.38 (s, 3 H).

Example 683
5-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]naphthalene-1-sulfonic acid
The title compound was prepared according to general procedure 9 from 5-(2-aminoethylamino)naphthalene-1-sulfonic acid and intermediate 24. LCMS $[M+H]^+$ 484.

Example 684
6-(3-chloro-2-methyl-phenyl)-N4-[2-(cyclopropylmethoxy)ethyl]pyrimidine-2,4-diamine
The title compound was prepared according to general procedure 9 from 2-(cyclopropylmethoxy)ethanamine and intermediate 24. LCMS $[M+H]^+$ 333. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.57 - 7.63 (m, 1 H), 7.32 - 7.39 (m, 2 H), 6.09 (s, 1 H), 3.70 - 3.74 (m, 2 H), 3.65 - 3.69 (m, 2 H), 3.34 - 3.37 (m, 2 H), 2.39 (s, 3 H), 1.05 (d, J=8.2 Hz, 1 H), 0.50 - 0.55 (m, 2 H), 0.19 - 0.24 (m, 2 H).

Example 685
2-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfanyl]pyrimidine-4-carboxamide
Step 1. A mixture of 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide (1 equiv.), 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide (1.2 equiv.), and Hünig's base (2 equiv.) in 2-propanol was stirred at 150 °C for 30 min. Thereafter the mixture was concentrated and purified by silica gel chromatography which afforded 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide. LCMS $[M+H]^+$ 299. ^{1}H NMR (400 MHz, CHLOROFORM-d) d ppm 8.80 (br. s., 1 H), 8.74 (d, J=5.1 Hz, 1 H), 7.80 (d, J=4.7 Hz, 1 H), 5.67 (br. s., 1 H), 5.01 (br. s., 1 H), 3.44 - 3.52 (m, 2 H), 3.23 - 3.30 (m, 2 H), 1.45 (s, 9 H).

Step 2. A mixture of 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide and TFA was stirred at 20 °C for 1 h. Thereafter the mixture was concentrated to afford 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide which was used without purification in step 3.

Step 3. The title compound was prepared according to general procedure 9 from 2-(2-aminoethylsulfanyl)pyrimidine-4-carboxamide and intermediate 24. LCMS $[M+H]^+$ 416.

Example 686

6-(3-chloro-2-methyl-phenyl)-N4-(3,3-difluoroallyl)pyrimidine-2,4-diamine

The title compound was isolated as a side product in the synthesis of N4-(3-bromo-3,3-difluoro-propyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine (prepared in example 687). LCMS $[M+H]^+$ 311. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.61 (dd, J=7.1, 2.4 Hz, 1 H), 7.34 - 7.39 (m, 2 H), 6.03 (s, 1 H), 4.62 - 4.74 (m, 1 H), 4.13 (dt, J=7.7, 1.8 Hz, 2 H), 2.38 (s, 3 H).

Example 687

N4-(3-bromo-3,3-difluoro-propyl)-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 3-bromo-3,3-difluoro-propan-1-amine and intermediate 24. LCMS $[M+H]^+$ 391. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.59 - 7.63 (m, 1 H), 7.32 - 7.40 (m, 2 H), 6.06 (s, 1 H), 3.81 (t, J=7.0 Hz, 2 H), 2.79 - 2.92 (m, 2 H), 2.38 (s, 3 H).

Example 688

6-(3-chloro-2-methyl-phenyl)-N4-[2-[[5-[(dimethylamino)methyl]-2-furyl]methylsulfanyl]ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-[[5-[(dimethylamino)methyl]-2-furyl]methylsulfanyl]ethanamine and intermediate 24. LCMS $[M+H]^+$ 432.

Example 689

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine

Step 1. A mixture of 1-(chloromethyl)-4-methylsulfonyl-benzene (1 equiv.), tert-butyl N-(2-sulfanylethyl)carbamate (1 equiv.), and Cs_2CO_3 (1 equiv.) was stirred in DMF at 60 °C for 16 h. Then the mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography to afford tert-butyl N-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]carbamate. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.90 (d, J=8.5 Hz, 2 H), 7.55 (d, J=8.5 Hz, 2 H), 3.80 (s, 2 H), 3.27 - 3.35 (m, 2 H), 3.07 (s, 3 H), 2.55 (t, J=6.8 Hz, 2 H), 1.46 (s, 9 H).

Step 2. A mixture of tert-butyl N-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]carbamate and TFA was stirred at 20 °C for 1 h. Thereafter the mixture was concentrated to afford 2-[(4-methylsulfonylphenyl)methylsulfanyl]ethanamine which was used without purification in step 3.

Step 3. A mixture of 2-[(4-methylsulfonylphenyl)methylsulfanyl]ethanamine (1 equiv.), 4,6-dichloropyrimidin-2-amine (1 equiv.), and Hünig's base (3 equiv.) was stirred in 2-propanol at 120 °C for 16 h. Then the mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography to afford 6-chloro-N4-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine.

Step 4. The title compound was prepared according to general procedure 2 from 6-chloro-N4-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine and (3-chloro-2-methyl)phenylboronic acid. LCMS $[M+H]^+$ 463. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.88 - 7.93 (m, 2 H), 7.52 - 7.56 (m, 2 H), 7.39 (dd, J=7.1, 2.4 Hz, 1 H), 7.14 - 7.21 (m, 2 H), 5.78 (s, 1 H), 4.98 - 5.06 (m, 1 H), 4.84 (s, 2 H), 3.82 (s, 2 H), 3.49 - 3.58 (m, 2 H), 3.06 (s, 3 H), 2.68 (t, J=6.5 Hz, 2 H), 2.37 (s, 3 H).

Example 690

6-(3-chloro-2-methylphenyl)-N4-{2-[(2-phenylethyl)sulfanyl]ethyl}pyrimidine-2,4-diamine

Step 1. A mixture of 2-bromoethylbenzene (1 equiv.), tert-butyl N-(2-sulfanylethyl)carbamate (1 equiv.), and Cs_2CO_3 (1 equiv.) was stirred in DMF at 60 °C for 16 h. Then the mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried ($MgSO_4$), concentrated, and purified

by silica gel chromatography to afford tert-butyl N-[2-(2-phenylethylsulfanyl)ethyl]carbamate. LCMS $[M+H]^+$ 282. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.28 - 7.34 (m, 2 H), 7.19 - 7.26 (m, 3 H), 3.32 (d, J=6.3 Hz, 2 H), 2.86 - 2.92 (m, 2 H), 2.77 - 2.84 (m, 2 H), 2.66 (t, J=6.5 Hz, 2 H), 1.43 - 1.47 (m, 9 H).

Step 2. A mixture of tert-butyl N-[2-(2-phenylethylsulfanyl)ethyl]carbamate and TFA was stirred at 20 °C for 1 h. Thereafter the mixture was concentrated to afford 2-(2-phenylethylsulfanyl)ethanamine which was used without purification in step 3.

Step 3. A mixture of 2-(2-phenylethylsulfanyl)ethanamine (1 equiv.), 4,6-dichloropyrimidin-2-amine (1 equiv.), and Hünig's base (3 equiv.) was stirred in 2-propanol at 120 °C for 16 h. Then the mixture was poured into sat. NaHCO3 and extracted with DCM ×3. The combined organics were dried (MgSO4), concentrated, and purified by silica gel chromatography to afford 6-chloro-N4-[2-(2-phenylethylsulfanyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 309.

Step 4. The title compound was prepared according to general procedure 2 from 6-chloro-N4-[2-(2-phenylethylsulfanyl)ethyl]pyrimidine-2,4-diamine and (3-chloro-2-methyl)phenylboronic acid. LCMS $[M+H]^+$ 399. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.38 (dd, J=7.6, 1.9 Hz, 1 H), 7.28 - 7.33 (m, 2 H), 7.13 - 7.25 (m, 4 H), 5.78 (s, 1 H), 5.03 - 5.16 (m, 1 H), 4.83 (br. s., 2 H), 3.54 (d, J=5.1 Hz, 2 H), 2.88 - 2.95 (m, 2 H), 2.80 - 2.86 (m, 2 H), 2.77 (t, J=6.6 Hz, 2 H), 2.36 (s, 3 H).

Example 691

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(4-methylsulfonylphenyl)methylsulfinyl]ethyl]pyrimidine-2,4-diamine

A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine (example 689) (1 equiv.) and H_2O_2 (3 equiv.) in MeOH was stirred at 20 °C for 2 h. Thereafter the mixture was concentrated and purified by silica gel chromatography to afford the title compound. LCMS $[M+H]^+$ 479. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.95 - 8.00 (m, 2 H), 7.51 - 7.55 (m, 2 H), 7.36 - 7.40 (m, 1 H), 7.13 - 7.19 (m, 2 H), 5.81 (s, 1 H), 5.37 (t, J=5.7 Hz, 1 H), 4.92 (s, 2 H), 4.16 (d, J=13.0 Hz, 1 H), 4.04 (d, J=13.3 Hz, 1 H), 3.83 - 4.01 (m, 2 H), 3.09 - 3.17 (m, 1 H), 3.08 (s, 3 H), 2.84 (dt, J=13.1, 5.1 Hz, 1 H), 2.36 (s, 3 H).

Example 692

6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-phenylethylsulfinyl)ethyl]pyrimidine-2,4-diamine

A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-phenylethylsulfanyl)ethyl]pyrimidine-2,4-diamine (example 690) (1 equiv.) and H_2O_2 (4 equiv.) in MeOH was stirred at 20 °C for 2 h. Thereafter the mixture was concentrated and purified by silica gel chromatography to afford the title compound. LCMS $[M+H]^+$ 415. ^{1}H NMR(400 MHz, CHLOROFORM-d) δ ppm 7.34 - 7.38 (m, 1 H), 7.30 - 7.34 (m, 2 H), 7.21 - 7.28 (m, 4 H), 7.11 - 7.19 (m, 2 H), 5.80 (s, 1 H), 5.61 (br. s., 1 H), 4.97 (s, 2 H), 3.93 (d, J=5.4 Hz, 2 H), 3.03 - 3.19 (m, 4 H), 2.87 - 3.02 (m, 2 H), 2.35 (s, 3 H).

Example 693

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(4-methylsulfonylphenyl)methylsulfonyl]ethyl]pyrimidine-2,4-diamine

A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-[(4-methylsulfonylphenyl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine (example 691) (1 equiv.) and 3-chloroperbenzoic acid (1.5 equiv.) in DCM was stirred at 20 °C for 1 h. The mixture was concentrated and purified by silica gel chromatography to afford the title compound. LCMS $[M+H]^+$ 495. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.97 - 8.02 (m, 2 H), 7.58 - 7.63 (m, 2 H), 7.37 - 7.40 (m, 1 H), 7.13 - 7.21 (m, 2 H), 5.84 (s, 1 H), 5.24 (t, J=6.2 Hz, 1 H), 4.90 (s, 2 H), 4.36 (s, 2 H), 3.96 (q, J=6.2 Hz, 2 H), 3.30 (t, J=6.0 Hz, 2 H), 3.08 (s, 3 H), 2.36 (s, 3 H).

Example 694

6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-phenylethylsulfonyl)ethyl]pyrimidine-2,4-diamine

A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-phenylethylsulfanyl)ethyl]pyrimidine-2,4-diamine (example 692) (1 equiv.) and 3-chloroperbenzoic acid (1.5 equiv.) in DCM was stirred at 20 °C for 1 h. The mixture was concentrated and purified by silica gel chromatography to afford the title compound. LCMS $[M+H]^+$ 431. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.36 - 7.40 (m, 1 H), 7.24 - 7.35 (m, 3 H), 7.18 - 7.22 (m, 2 H), 7.13 - 7.18

(m, 2 H), 5.81 (s, 1 H), 5.26 (t, J=6.0 Hz, 1 H), 4.87 (s, 2 H), 3.94 (q, J=6.2 Hz, 2 H), 3.28 - 3.34 (m, 2 H), 3.24 (t, J=6.0 Hz, 2 H), 3.14 - 3.19 (m, 2 H), 2.35 (s, 3 H).

Example 695

Isopropyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

Step 1. A mixture of 2-(4-carboxyphenyl)ethylammonium chloride (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in 2-propanol at reflux for 16h. The mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude isopropyl 4-(2-aminoethyl)benzoate was used in step 2 without further purification. LCMS $[M+H]^+$ 208.

Step 2. The title compound was prepared according to general procedure 9 from isopropyl 4-(2-aminoethyl)benzoate and intermediate 24. LCMS $[M+H]^+$ 425. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.88 (d, J=8.2 Hz, 2 H), 7.42 (d, J=8.2 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 7.20 - 7.27 (m, 2 H), 7.06 (br. s., 1 H), 6.06 (br. s., 2 H), 5.84 (s, 1 H), 5.13 (spt, J=6.3 Hz, 1 H), 3.52 (br. s., 2 H), 2.92 (t, J=7.4 Hz, 2 H), 2.38 (s, 3 H), 1.32 (d, J=6.3 Hz, 6 H).

Example 696

1-[3-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]phenyl]guanidine

A mixture of Intermediate 47 (1 equiv.) and tert-butyl (N2)-N-[(tert-butoxycarbonylamino)-pyrazol-1-yl-methylene]carbamate (1.4 equiv.) in 2-propanol was stirred at 150 °C for 1 h. The mixture was then concentrated and thereafter dissolved in TFA. The resulting mixture was stirred at 150 °C for 30 min. after which it was concentrated and purified by preparative LC. $[M+H]^+$ 396. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.63 (m, 1 H), 7.41 - 7.47 (m, 1 H), 7.29 - 7.38 (m, 3 H), 7.22 (t, J=1.7 Hz, 1 H), 7.17 (ddd, J=7.9, 2.2, 1.3 Hz, 1 H), 6.02 (s, 1 H), 3.80 (t, J=7.3 Hz, 2 H), 3.01 (t, J=7.3 Hz, 2 H), 2.38 (s, 3 H).

Example 697

4-(2-(2-Amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)-1-hydroxyethyl)benzenesulfonamide

Step 1: 4-(2-Bromoacetyl)benzenesulfonamide

Br_2 (7.2 g, 45.0 mmol, in 10 mL HOAc) was added dropwise to the solution of 4-acetylbenzenesulfonamide (9.0 g, 45.0 mmol) in HOAc (250 mL) at 40 °C. The reaction mixture was stirred for 1 h at 40 °C. After removal of solvent under reduced pressure, the residue was purified by recrystallization from EtOH (20 mL) to yield the product (6.60 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.99 (s, 2 H), 7.59 (s, 2 H), 7.98 (m, 2 H), 8.16 (m, 2 H) ppm. LC-MS (ESI): *m/z* 277.93 $[M+H]^+$.

Step 2: 4-(2-Bromo-1-hydroxyethyl)benzenesulfonamide

To the mixture of 4-(2-Bromoacetyl)benzenesulfonamide (1.00 g, 3.6 mmol) in THF (20 mL) was added borane-dimethylsulphide complex (0.33 g, 4.3 mmol) at 0 °C. The mixture was stirred for 24 h. at R.T. After removal of solvent under reduced pressure, the residue was purified by column chromatography to afford the product (0.30 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (m, 1 H), 3.72 (m, 1 H), 4.91 (m, 1 H), 6.00 (d, *J* = 4.8 Hz, 1 H), 7.34 (s, 2 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H) ppm.

Step 3: 4-(2-Amino-1-hydroxyethyl)benzenesulfonamide

The mixture of 4-(2-Bromo-1-hydroxyethyl)benzenesulfonamide (0.30 g, 1.1 mmol) and NH_4OH (15 mL) was stirred for 60 h. at R.T. Removal of solvent under reduced pressure afforded the crude product as a yellow solid (100 %), which was used for next step without further purification. ^{1}H NMR (400 MHz, D_2O): δ 3.08 (m, 1 H), 3.24 (m, 1 H), 4.99 (m, 1 H), 7.54 (m, 2 H), 7.82 (m, 2 H) ppm.

Step 4: 4-(2-(2-Amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)-1-hydroxyethyl)benzenesulfonamide

The amine prepared in step 3 above (0.23 g, 1.0 mmol), and intermediate 24 (0.27 g, 1.0 mmol) and NEt_3 (0.20 g, 2.0 mmol) in *i*-PrOH (12 mL) was stirred at 95 °C overnight. After removal of solvent, the residue was purified by preparative HPLC to afford the target compound as a white solid (44 mg, 0.10 mmol, 10 %, purity 99.8 %). ^{1}H NMR (400 MHz, D_2O): δ = 2.29 (s, 3 H), 3.22 (m, 1 H), 3.31 (s, 1 H), 3.61 (br, 1 H), 4.86 (s, 1 H), 5.77 (m, 1 H), 5.83 (s, 1 H), 6.12 (s, 2 H), 7.21 (m, 2 H), 7.27 (s, 1 H), 7.43 (m, 1 H), 7.59 (m, 2 H), 7.81 (m, 2 H) ppm.

Example 698

6-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfanyl]pyridine-3-sulfonamide

Step 1. A mixture of 6-chloropyridine-3-sulfonamide (1 equiv.), tert-butyl N-(2-sulfanylethyl)carbamate (1.2 equiv.), and Hünig's base (2 equiv.) in 2-propanol was stirred at 120 °C for 16 h. The mixture was then concentrated, dissolved in DCM and passed through a short plug of silica. After concentration the crude residue was used without further purification in step 2.

Step 2. The crude residue from step 1 was stirred in TFA at 20 °C for 2 h. The TFA was then removed by co-evaporation with 2-propanol. Used without further purification in step 3. LCMS $[M+H]^+$ 234.

Step 3. The title compound was prepared according to general procedure 9 from the material from step 2 and intermediate 24. LCMS [M+H]+ 451.

Example 699

methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfanylmethyl]benzoate

Step 1. A mixture of methyl 4-(bromomethyl)benzoate (1 equiv.), tert-butyl N-(2-sulfanylethyl)carbamate (1.3 equiv.), and K_2CO_3 (1.1 equiv.) were stirred in DMF at 60 °C for 16 h. The mixture was poured into water and extracted with DCM ×3. The combined organics were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography to afford methyl 4-[2-(tert-butoxycarbonylamino)ethylsulfanylmethyl]benzoate.

Step 2. Methyl 4-[2-(tert-butoxycarbonylamino)ethylsulfanylmethyl]benzoate was stirred in TFA at 20 °C for 2 h. The TFA was then removed by co-evaporation with 2-propanol. Used without further purification in step 3.

Step 3. The title compound was prepared according to general procedure 9 from the material from step 2 and intermediate 24. LCMS $[M+H]^+$ 443. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.94 - 7.98 (m, 2 H), 7.60 (dd, J=7.0, 2.5 Hz, 1 H), 7.47 - 7.51 (m, 2 H), 7.33 - 7.37 (m, 2 H), 6.02 (s, 1 H), 3.89 (s, 3 H), 3.87 (s, 2 H), 3.66 (t, J=6.8 Hz, 2 H), 2.71 (t, J=6.8 Hz, 2 H), 2.38 (s, 3 H).

Example 700

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(5-methylisoxazol-3-yl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine

Step 1. A mixture of 3-(chloromethyl)-5-methyl-isoxazole (1 equiv.), tert-butyl N-(2-sulfanylethyl)carbamate (1.3 equiv.), and K_2CO_3 (1.1 equiv.) were stirred in DMF at 60 °C for 16 h. The mixture was poured into water and extracted with

DCM ×3. The combined organics were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography to afford tert-butyl N-[2-[(5-methylisoxazol-3-yl)methylsulfanyl]ethyl]carbamate.

Step 2. Tert-butyl N-[2-[(5-methylisoxazol-3-yl)methylsulfanyl]ethyl]carbamate was stirred in TFA at 20 °C for 2 h. The TFA was then removed by co-evaporation with 2-propanol. Used without further purification in step 3.

Step 3. The title compound was prepared according to general procedure 9 from the material from step 2 and intermediate 24. LCMS $[M+H]^+$ 390. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.62 (m, 1 H), 7.34 - 7.37 (m, 2 H), 6.18 (d, J=0.9 Hz, 1 H), 6.05 (s, 1 H), 3.77 (s, 2 H), 3.70 (t, J=6.8 Hz, 2 H), 2.73 (t, J=6.8 Hz, 2 H), 2.40 (d, J=0.9 Hz, 3 H), 2.39 (s, 3 H).

Example 701

6-(3-chloro-2-methyl-phenyl)-N4-[2-(3,5-dimethylisoxazol-4-yl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(3,5-dimethylisoxazol-4-yl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 358. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.60 (dd, J=7.4, 1.4 Hz, 1 H), 7.34 - 7.38 (m, 1 H), 7.31 - 7.34 (m, 1 H), 5.99 (s, 1 H), 3.68 (t, J=7.0 Hz, 2 H), 2.71 (t, J=6.8 Hz, 2 H), 2.37 (s, 3 H), 2.33 (s, 3 H), 2.26 (s, 3 H).

Example 702

6-(3-chloro-2-methyl-phenyl)-N4-propyl-pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from propan-1-amine and intermediate 24. LCMS $[M+H]^+$ 277. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.56 - 7.62 (m, 1 H), 7.32 - 7.38 (m, 2 H), 6.03 (s, 1 H), 3.45 - 3.51 (m, 2 H), 2.38 (s, 3 H), 1.62 - 1.73 (m, 2 H), 0.97 - 1.03 (m, 3 H).

Example 703

N4-butyl-6-(3-chloro-2-methyl-phenyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from butan-1-amine and intermediate 24. LCMS $[M+H]^+$ 291. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.63 (m, 1 H), 7.32 - 7.38 (m, 2 H), 6.02 (s, 1 H), 3.52 (t, J=7.1 Hz, 2 H), 2.38 (s, 3 H), 1.59 - 1.68 (m, 2 H), 1.38 - 1.49 (m, 2 H), 0.96 - 1.02 (m, 3 H).

Example 704

6-(3-chloro-2-methyl-phenyl)-N4-(2-methoxyethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-methoxyethanamine and intermediate 24. LCMS $[M+H]^+$ 293. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.62 (m, 1 H), 7.32 - 7.39 (m, 2 H), 6.08 (s, 1 H), 3.69 - 3.73 (m, 2 H), 3.57 - 3.62 (m, 2 H), 3.39 (s, 3 H), 2.38 (s, 3 H).

Example 705

6-(3-chloro-2-methyl-phenyl)-N4-(3-ethoxypropyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 3-ethoxypropan-1-amine and intermediate 24. LCMS $[M+H]^+$ 321. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.63 (m, 1 H), 7.32 - 7.39 (m, 2 H), 6.03 (s, 1 H), 3.60 (t, J=7.0 Hz, 2 H), 3.47 - 3.56 (m, 4 H), 2.38 (s, 3 H), 1.87 - 1.94 (m, 2 H), 1.17 - 1.22 (m, 3 H).

Example 706

6-(3-chloro-2-methyl-phenyl)-N4-(tetrahydropyran-4-ylmethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from tetrahydropyran-4-ylmethanamine and intermediate 24. LCMS $[M+H]^+$ 333.

Example 707

6-(3-chloro-2-methyl-phenyl)-N4-(tetrahydrofuran-2-ylmethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from tetrahydrofuran-2-ylmethanamine and intermediate 24. LCMS $[M+H]^+$ 319. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.62 (m, 1 H), 7.32 - 7.39 (m, 2 H), 6.09 (s, 1 H), 4.12 (dd, J=7.0, 4.4 Hz, 1 H), 3.87 - 3.95 (m, 1 H), 3.74 - 3.81 (m, 1 H), 3.63 - 3.70 (m, 1 H), 3.54 - 3.61 (m, 1 H), 2.39 (s, 3 H), 2.00 - 2.11 (m, 1 H), 1.96 (dtd, J=7.7, 6.5, 6.5, 1.4 Hz, 2 H), 1.65 (dd, J=12.0, 8.5 Hz, 1 H).

Example 708

6-(3-chloro-2-methyl-phenyl)-N4-[(2E)-3,7-dimethylocta-2,6-dienyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from geranylamine and intermediate 24. LCMS $[M+H]^+$ 371. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.58 - 7.61 (m, 1 H), 7.31 - 7.38 (m, 2 H), 6.02 (s, 1 H), 5.30 - 5.36 (m, 1 H), 5.11 (ddt, J=8.2, 5.5, 1.5, 1.5 Hz, 1 H), 4.12 (dd, J=7.0, 0.6 Hz, 2 H), 2.38 (s, 3 H), 2.09 (s, 4 H), 1.76 (d, J=1.3 Hz, 3 H), 1.67 (d, J=1.3 Hz, 3 H), 1.61 (d, J=0.6 Hz, 3 H).

Example 709

6-(3-chloro-2-methyl-phenyl)-N4-isobutyl-pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from isobutylamine and intermediate 24. LCMS $[M+H]^+$ 291. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.57 - 7.62 (m, 1 H), 7.33 - 7.39 (m, 2 H), 6.05 (s, 1 H), 3.36 (d, J=7.0 Hz, 2 H), 2.39 (s, 3 H), 1.96 (dquin, J=13.6, 6.8, 6.8, 6.8, 6.8 Hz, 1 H), 1.00 (s, 3 H), 0.98 (s, 3 H).

Example 710

methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

Step 1. A mixture of 2-(4-carboxyphenyl)ethylammonium chloride (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in methanol at reflux for 16h. The mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried (MgSO4) and concentrated. The crude methyl 4-(2-aminoethyl)benzoate was used in step 2 without further purification. LCMS [M+H]+ 180.

Step 2. The title compound was prepared according to general procedure 9 from methyl 4-(2-aminoethyl)benzoate and intermediate 24. LCMS $[M+H]^+$ 397. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.94 (d, J=8.2 Hz, 2 H), 7.35 - 7.43 (m, 3 H), 7.13 - 7.25 (m, 2 H), 5.76 (s, 1 H), 3.89 (s, 3 H), 3.60 - 3.71 (m, 2 H), 2.98 (t, J=7.1 Hz, 2 H), 2.30 (s, 3 H).

Example 711

ethyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

Step 1. A mixture of 2-(4-carboxyphenyl)ethylammonium chloride (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in ethanol at reflux for 16h. The mixture was poured

into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried ($MgSO_4$) and concentrated. The crude ethyl 4-(2-aminoethyl)benzoate was used in step 2 without further purification. LCMS [M+H]+ 194.

Step 2. The title compound was prepared according to general procedure 9 from ethyl 4-(2-aminoethyl)benzoate and intermediate 24. LCMS $[M+H]^+$ 411. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.94 (d, J=8.2 Hz, 2 H), 7.35 - 7.43 (m, 3 H), 7.13 - 7.24 (m, 2 H), 5.75 (s, 1 H), 4.35 (q, J=7.3 Hz, 2 H), 3.64 (br. s., 2 H), 2.98 (t, J=7.1 Hz, 2 H), 2.30 (s, 3 H), 1.38 (t, J=7.1 Hz, 3 H).

Example 712

propyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

Step 1. A mixture of 2-(4-carboxyphenyl)ethylammonium chloride (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in 1-propanol at 90 °C for 16h. The mixture was poured into sat. $NaHCO_3$ and extracted with DCM ×3. The combined organics were dried (MgSO4) and concentrated. The crude propyl 4-(2-aminoethyl)benzoate was used in step 2 without further purification. LCMS [M+H]+ 208.

Step 2. The title compound was prepared according to general procedure 9 from propyl 4-(2-aminoethyl)benzoate and intermediate 24. LCMS $[M+H]^+$ 425. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.95 (d, J=8.2 Hz, 2 H), 7.36 - 7.43 (m, 3 H), 7.14 - 7.24 (m, 2 H), 5.76 (s, 1 H), 4.23 - 4.29 (m, 2 H), 3.60 - 3.70 (m, 2 H), 2.99 (t, J=7.1 Hz, 2 H), 2.30 (s, 3 H), 1.73 - 1.85 (m, 2 H), 1.04 (t, J=7.4 Hz, 3 H).

Example 713

6-(3-chloro-2-methyl-phenyl)-N4-(2-phenylethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-phenylethanamine and intermediate 24. LCMS $[M+H]^+$ 339.

Example 714

6-(3-chloro-2-methyl-phenyl)-N4-[2-(4-pyridyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(4-pyridyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 340. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.53 - 8.58 (m, 2 H), 7.39 (dd, J=7.6, 1.9 Hz, 1 H), 7.13

- 7.22 (m, 2 H), 5.77 (s, 1 H), 4.83 (br. s., 2 H), 4.69 - 4.77 (m, 1 H), 3.65 (br. s., 2 H), 2.94 (t, J=7.0 Hz, 2 H), 2.37 (s, 3 H).

Example 715

6-(3-chloro-2-methyl-phenyl)-N4-[2-(2-pyridyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(2-pyridyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 340. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.51 - 8.57 (m, 1 H), 7.63 (td, J=7.7, 1.9 Hz, 1 H), 7.37 (dd, J=7.6, 1.6 Hz, 1 H), 7.12 - 7.22 (m, 4 H), 5.79 (s, 1 H), 5.56 (t, J=5.2 Hz, 1 H), 4.87 (br. s., 2 H), 3.70 - 3.81 (m, 2 H), 3.09 (t, J=6.6 Hz, 2 H), 2.36 (s, 3 H).

Example 716

2-hydroxyethyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoic acid (prepared in example 485) (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in ethylene glycol at 120 °C for 2 h. The mixture was then purified by preparative LC. LCMS $[M+H]^+$ 427.

Example 717

2-methylsulfonylethyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoic acid (prepared in example 485) (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in 2-methylsulfonylethanol at 120 °C for 2 h. The mixture was then purified by preparative LC. LCMS $[M+H]^+$ 489.

Example 718

2,3-dihydroxypropyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoate

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzoic acid (prepared in example 485) (1 equiv.) and H_2SO_4 (1 equiv.) was stirred in glycerol at 120 °C for 2 h. The mixture was then purified by preparative LC. LCMS $[M+H]^+$ 457.

Example 719

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(6-methylsulfonyl-3-pyridyl)amino]ethyl]pyrimidine-2,4-diamine

Step 1. N'-(6-methylsulfonyl-3-pyridyl)ethane-1,2-diamine was prepared according to general procedure 13 from 5-bromo-2-methylsulfonyl-pyridine and ethylenediamine.

Step 2. The title compound was prepared according to general procedure 9 from N'-(6-methylsulfonyl-3-pyridyl)ethane-1,2-diamine and intermediate 24. LCMS $[M+H]^+$ 433. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 8.11 (d, J=2.8 Hz, 1 H), 7.83 (d, J=8.8 Hz, 1 H), 7.60 (dd, J=7.6, 1.6 Hz, 1 H), 7.30 - 7.39 (m, 2 H), 7.15 (dd, J=8.8, 2.8 Hz, 1 H), 6.03 (s, 1 H), 3.73 - 3.79 (m, 2 H), 3.53 (t, J=6.3 Hz, 2 H), 3.10 (s, 3 H), 2.37 (s, 3 H).

Example 720

N-[4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylamino]-2-methyl-phenyl]acetamide

Step 1. N-[4-(2-aminoethylamino)- 2-methyl-phenyl]acetamide was prepared according to general procedure 13 from N-(4-iodo-2-methyl-phenyl)acetamide and ethylenediamine.

Step 2. The title compound was prepared according to general procedure 9 from N-[4-(2-aminoethylamino)- 2-methyl-phenyl]acetamide and intermediate 24. LCMS $[M+H]^+$ 425. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.61 (dd, J=7.6, 1.6 Hz, 1 H), 7.30 - 7.40 (m, 2 H), 7.15 (d, J=8.2 Hz, 1 H), 6.75 (d, J=12.6 Hz, 2 H), 6.05 (s, 1 H), 3.77 (t, J=6.0 Hz, 2 H), 3.50 (d, J=5.1 Hz, 2 H), 2.38 (s, 3 H), 2.19 (s, 3 H), 2.13 (s, 3 H).

Example 721

6-(3-chloro-2-methyl-phenyl)-N4-[(2Z)-2-(fluoromethylene)-4-(4-fluorophenyl)butyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from (2Z)-2-(fluoromethylene)-4- (4-fluorophenyl)butan-1-ammonium chloride and intermediate 24. LCMS $[M+H]^+$ 415. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.41 (dd, J=7.4, 2.1 Hz, 1 H), 7.14 - 7.25 (m, 5 H), 6.94 (t, J=8.7 Hz, 2 H), 6.69 (d, J=85.0 Hz, 1 H), 5.80 (s, 1 H), 3.95 (br. s., 2 H), 2.74 - 2.81 (m, 2 H), 2.39 - 2.46 (m, 2 H), 2.31 (s, 3 H).

Example 722

Step 1 2-Bromo-5-(methylsulfonyl)pyridine

Isopropylmagnesium chloride (2.0 M, 13.7 mL, 27.4 mmol) was added to a solution of 3,6-dibromopyridine (5.00 g, 21.1 mmol) in THF (18 mL) at 0 °C at a rate which maintained the temperature below 8 °C. The reaction mixture was stirred at 0 °C for 45 min. At -15 °C the solution of methanesulfonyl chloride (3.22 g, 28.1 mmol) in THF (4 mL) was added at a rate which maintained the temperature below 5 °C. The reaction mixture was allowed to warm up to room temperature and then quenched by adding water (50 mL) and ethyl acetate (30 mL) to it. After separation, the organic layer was dried over Na_2SO_4. After removal of solvent, the residue was purified by column chromatography to afford the expected product (2.4 g). 1H NMR (400 MHz, DMSO-d6): δ = 3.37 (s, 3 H), 7.98 (m, 1 H), 8.26 (m, 1 H), 8.89 (d, J = 0.4 Hz, 1 H) ppm.

Step 2 6-(3-Chloro-2-methylphenyl)-N4-(2-(5-(methylsulfonyl)pyridin-2-yloxy)ethyl)pyrimidine-2,4-diamine

NaH (60% , 86 mg, 2.154 mmol) was added to the solution of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol (intermediate 55) (337 mg, 1.44 mmol) in THF (15 mL). The reaction mixture was stirred for 10 min at RT. After addition of Bromo-5-(methylsulfonyl)pyridine (200 mg, 0.72 mmol), the reaction mixture was stirred for 30 min at RT. The reaction was quenched by adding 6 drops of water. After removal of solvent under reduced pressure, the residue was purified by prep HPLC (eluent: mixture of MeCN and 0.1 % aqueous NH_4HCO_3 solution) to afford the product. 1H NMR (400 MHz, DMSO-d6): δ = 2.29 (s, 3 H), 3.26 (s, 3 H), 3.69 (s, 2 H), 4.50 (t, J = 6.4 Hz, 2 H), 5.78 (s, 1 H), 6.11 (s, 2 H), 7.19 (m, 1 H), 7.22 (m, 3 H), 7.44 (m, 1 H), 8.19 (m, 1 H), 8.67 (s, 1 H) ppm.

Example 723

(2-(2-Amino-6-(4-(methylsulfonyl)phenethylamino)pyrimidin-4-yl)-6-chlorophenyl)methanol

The solution of (2-(2-Amino-6-chloropyrimidin-4-yl)-6-chlorophenyl)methanol (prepared in example 750; step 2) (55.3 mg, 0.21 mmol), 2-(4-methanesulfonylphenyl)ethan-1-amine (104 mg, 0.45 mmol) and DIPEA (86.3 mg, 0.67 mmol) in *n*-BuOH (3 mL) was stirred overnight under reflux. After

removal the solvent under the reduced pressure, the residue was purified by preparative HPLC to give the product (14.2 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.97 (t, J = 7.5 Hz, 2 H), 3.19 (s, 3 H), 3.31 (s, 1 H), 3.54 (m, 2 H), 4.45 (s, 2 H), 5.95 (br, 1 H), 6.34 (s, 1 H), 7.38 (m, 2 H), 7.55 (m, 3 H), 7.86 (m, 2 H) ppm.

Example 724

methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfinylmethyl]benzoate

A mixture of methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfanylmethyl]benzoate (example 699) (1 equiv.) and H_2O_2 (5 equiv.) in MeOH was stirred at 20 °C for 16 h. Thereafter the mixture was concentrated and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 459. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 8.03 - 8.06 (m, 2 H), 7.61 (dd, J=7.6, 1.9 Hz, 1 H), 7.49 - 7.53 (m, 2 H), 7.31 - 7.39 (m, 2 H), 6.06 (s, 1 H), 4.33 (d, J=13.0 Hz, 1 H), 4.19 (d, J=13.0 Hz, 1 H), 3.94 - 4.00 (m, 2 H), 3.23 (ddd, J=13.7, 7.7, 6.3 Hz, 1 H), 3.00 (dt, J=13.4, 5.4 Hz, 1 H), 2.37 (s, 3 H).

Example 725

6-(3-chloro-2-methyl-phenyl)-N4-[2-[(5-methylisoxazol-3-yl)methylsulfinyl]ethyl]pyrimidine-2,4-diamine

A mixture of 6-(3-chloro-2-methyl-phenyl)-N4-[2-[(5-methylisoxazol-3-yl)methylsulfanyl]ethyl]pyrimidine-2,4-diamine (example 700) (1 equiv.) and H_2O_2 (5 equiv.) in MeOH was stirred at 20 °C for 16 h. Thereafter the mixture was concentrated and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 406. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.61 (dd, J=7.0, 2.2 Hz, 1 H), 7.31 - 7.40 (m, 2 H), 6.25 (s, 1 H), 6.08 (s, 1 H), 4.34 (d, J=13.6 Hz, 1 H), 4.14 (d, J=13.9 Hz, 1 H), 3.94 - 4.00 (m, 2 H), 3.23 - 3.29 (m, 1 H), 3.09 (dt, J=13.5, 5.6 Hz, 1 H), 2.45 (s, 3 H), 2.38 (s, 3 H).

Example 726

6-(3-chloro-2-methyl-phenyl)-N4-[2-(4-ethylphenyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(4-ethylphenyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 367. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.59 (dd, J=7.6, 1.9 Hz, 1 H), 7.30 - 7.38 (m, 2 H),

7.12 - 7.20 (m, 4 H), 6.00 (s, 1 H), 3.75 (t, J=7.3 Hz, 2 H), 2.91 (t, J=7.3 Hz, 2 H), 2.61 (q, J=7.6 Hz, 2 H), 2.37 (s, 3 H), 1.20 (t, J=7.6 Hz, 3 H).

Example 727

4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzene-1,2-diol

The title compound was prepared according to general procedure 9 from 2-(3,4-dihydroxyphenyl)ethylamine hydrochloride and intermediate 24. LCMS $[M+H]^+$ 371.

Example 728

5-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethyl]benzene-1,2,3-triol

The title compound was prepared according to general procedure 9 from 2-(3,4,5-trihydroxyphenyl)ethylamine hydrochloride and intermediate 24. LCMS $[M+H]^+$ 387. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.56 - 7.62 (m, 1 H), 7.30 - 7.38 (m, 2 H), 6.24 (s, 2 H), 6.00 (s, 1 H), 3.65 - 3.72 (m, 2 H), 2.73 (t, J=7.1 Hz, 2 H), 2.38 (s, 3 H).

Example 729

6-(3-chloro-2-methyl-phenyl)-N4-(2-methylallyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-methylprop-2-en-1-amine and intermediate 24. LCMS $[M+H]^+$ 289.

Example 730

methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfonylmethyl]benzoate

A mixture of methyl 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethylsulfinylmethyl]benzoate (example 724) (1 equiv.) and 3-chloroperbenzoic acid (1.5 equiv.) in DCM was stirred at 20 °C for 2 h. The mixture was concentrated and purified by silica gel chromatography to afford the title compound. LCMS $[M+H]^+$ 475. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 8.00 - 8.04 (m, 2 H), 7.53 - 7.57 (m, 2 H), 7.42 (dd, J=7.1, 2.1 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 5.85 (s, 1 H), 4.55 (s, 2 H), 3.91 (s, 3 H), 3.85 (t, J=6.5 Hz, 2 H), 3.37 (t, J=6.3 Hz, 2 H), 2.32 (s, 3 H).

Example 731

methyl 4-[[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]methyl]cyclohexanecarboxylate

The title compound was prepared according to general procedure 9 from methyl 4-(aminomethyl)cyclohexanecarboxylate and intermediate 24. LCMS $[M+H]^+$ 389. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 7.37 - 7.44 (m, 1 H), 7.16 - 7.24 (m, 2 H), 5.81 (s, 1 H), 3.65 (s, 3 H), 3.14 - 3.28 (m, 2 H), 2.25 - 2.34 (m, 4 H), 1.99 (br. s., 2 H), 1.86 - 1.94 (m, 2 H), 1.52 - 1.66 (m, 1 H), 1.41 (dd, J=12.6, 3.5 Hz, 2 H), 1.06 (d, J=3.5 Hz, 2 H).

Example 732

4-[4-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]but-2-ynylsulfanyl]benzoic acid

Step 1. A mixture of 3-sulfanylbenzoic acid (3 equiv.), 4-chlorobut-2-yn-1-amine hydrochloride (1 equiv.), and Hünig's base (6 equiv.) in 2-propanol was stirred at 120 °C for 16 h. A precipitate formed which was collected by filtration and washed with MeOH and DCM to afford 3-(4-aminobut-2-ynylsulfanyl)benzoic acid. LCMS $[M+H]^+$ 222.

Step 2. The title compound was prepared according to general procedure 9 from 3-(4-aminobut-2-ynylsulfanyl)benzoic acid and intermediate 24. LCMS $[M+H]^+$ 439. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 8.07 - 8.10 (m, 1 H), 7.85 - 7.88 (m, 1 H), 7.59 - 7.66 (m, 2 H), 7.39 - 7.45 (m, 1 H), 7.35 - 7.38 (m, 2 H), 6.03 (s, 1 H), 4.29 (t, J=2.1 Hz, 2 H), 3.78 (t, J=2.2 Hz, 2 H), 2.37 (s, 3 H).

Example 733

6-(3-chloro-2-methyl-phenyl)-N4-[2-(3-pyridyl)ethyl]pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-(3-pyridyl)ethanamine and intermediate 24. LCMS $[M+H]^+$ 340. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 8.85 (s, 1 H), 8.76 (d, J=5.7 Hz, 1 H), 8.59 (dt, J=7.8, 1.8 Hz, 1 H), 8.03 (dd, J=7.9, 5.7 Hz, 1 H), 7.58 - 7.62 (m, 1 H), 7.29 - 7.39 (m, 2 H), 6.03 (s, 1 H), 3.90 (t, J=6.8 Hz, 2 H), 3.24 (t, J=7.0 Hz, 2 H), 2.37 (s, 3 H).

Example 734

6-(3-chloro-2-methyl-phenyl)-N4-(2-pyrimidin-2-ylethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-pyrimidin-2-ylethanammonium chloride and intermediate 24. LCMS $[M+H]^+$ 341. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.65 - 10.54 (m, 2 H), 8.75 - 8.95 (m, 2 H), 7.48 (dd, J=7.7, 1.4 Hz, 1 H), 7.44 (br. s., 1 H), 7.37 (d, J=4.4 Hz, 1 H), 7.18 - 7.22 (m, 1 H), 7.14 - 7.17 (m, 1 H), 5.84 (s, 1 H), 4.04 (br. s., 2 H), 3.39 (br. s., 2 H), 2.32 (s, 3 H).

Example 735

6-(3-chloro-2-methyl-phenyl)-N4-(2-pyrazin-2-ylethyl)pyrimidine-2,4-diamine

The title compound was prepared according to general procedure 9 from 2-pyrazin-2-ylethanammonium chloride and intermediate 24. LCMS $[M+H]^+$ 341. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.47 - 8.62 (m, 3 H), 7.47 (dd, J=7.6, 1.6 Hz, 1 H), 7.34 (t, J=5.7 Hz, 1 H), 7.14 - 7.22 (m, 2 H), 5.84 (s, 1 H), 3.95 (q, J=6.0 Hz, 2 H), 3.18 (t, J=6.3 Hz, 2 H), 2.33 (s, 3 H).

Example 736

N4-[2-(4-bromophenyl)ethyl]-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (200 mg, 0.79 mmol; Intermediate 24), 2-(4-bromophenyl)ethan-1-amine (183 µL, 1.18 mmol) and triethylamine (200 µl, 1.43 mmol) in n-butanol (3 mL) was heated in a sealed tube at 120°C for 72 h. The mixture was left at r.t. for 4 h and the solid material was removed by filtration. The filtrate was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 417.

Example 737

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-(1-hydroxypropan-2-yl)benzamide

Step 1: A mixture of 4,6-dichloropyrimidin-2-amine (600 mg, 3.66 mmol), 4-(2-aminoethyl)benzoic acid hydrochloride (812 mg, 4.02 mmol) and triethylamine (1.53 mL, 10.98 mmol) in n-butanol (20 mL) was heated in a sealed tube at 110°C overnight and then concentrated. The residue was recrystallized from a mixture of 2-propanol, methanol and water. The solid material was collected by filtration and dried to give 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzoic acid. LCMS $[M+H]^+$ 293.

Step 2: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzoic

acid (58 mg, 0.20 mmol), 2-aminopropan-1-ol (30 µL, 0.39 mmol), HATU coupling reagent (91 mg, 0.24 mmol) and triethylamine (80 µL, 0.59 mmol) in DMF (3 mL) was stirred at r.t. for 2 h. Purified by preparative HPLC to give 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}-N-(1-hydroxypropan-2-yl)benzamide.

Step 3: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}-N-(1-hydroxypropan-2-yl)benzamide (40 mg, 0.11 mmol), (3-chloro-2-methylphenyl)boronic acid (25 mg, 0.15 mmol), $Pd(PPh_3)_4$ (7 mg, 0.010 mmol) and potassium carbonate (32 mg, 0.23 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 90°C overnight. The mixture was concentrated and purified by preparative HPLC to give 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-(1-hydroxypropan-2-yl)benzamide. LCMS $[M+H]^+$ 440.

Example 738

give 6-(3-chloro-2-methylphenyl)-4-N-{2-[4-(4-methylpiperazine-1-carbonyl)phenyl]ethyl}pyrimidine-2,4-diamine

Step 1: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzoic acid (59 mg, 0.20 mmol) prepared in example 737 step 1, 1-methylpiperazine (40 µL, 0.36 mmol), HATU coupling reagent (91 mg, 0.24 mmol) and triethylamine (80 µL, 0.59 mmol) in DMF (3 mL) was stirred at r.t. for 2 h. Purified by preparative HPLC to give 6-chloro-4-N-{2-[4-(4-methylpiperazine-1-carbonyl)phenyl]ethyl}pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 375.

Step 2: A mixture of 6-chloro-4-N-{2-[4-(4-methylpiperazine-1-carbonyl)phenyl]ethyl}pyrimidine-2,4-diamine (30 mg, 0.080 mmol), (3-chloro-2-methylphenyl)boronic acid (18 mg, 0.10 mmol), $Pd(PPh_3)_4$ (5 mg, 0.0043 mmol) and potassium carbonate (22 mg, 0.16 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 90°C overnight. The mixture was concentrated and purified by preparative HPLC to give 6-(3-chloro-2-methylphenyl)-4-N-{2-[4-(4-methylpiperazine-1-carbonyl)phenyl]ethyl}pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 465.

Example 739

6-(3-chloro-2-methylphenyl)-N4-[2-(4-methanesulfinylphenyl)ethyl]pyrimidine-2,4-diamine

Step 1: A mixture of 1-bromo-4-methanesulfinylbenzene (88 mg, 0.40 mmol),

potassium benzyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (160 mg, 0.56 mmol), caesium carbonate (261 mg, 0.80 mmol), $Pd(OAc)_2$ (9 mg, 0.040 mmol) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (37 mg, 0.080 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 100°C overnight. The mixture was concentrated and purified by preparative HPLC to give benzyl N-[2-(4-methanesulfinylphenyl)ethyl]carbamate. LCMS $[M+H]^+$ 318.

Step 2: Benzyl N-[2-(4-methanesulfinylphenyl)ethyl]carbamate (39 mg, 0.12 mmol) was heated in TFA (1 mL) at 70°C overnight. The mixture was concentrated and dried under vacuum to give 2-(4-methanesulfinylphenyl)ethan-1-amine; trifluoroacetic acid. LCMS $[M+H]^+$ 184.

Step 3: A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0.10 mmol; Intermediate 24), 2-(4-methanesulfinylphenyl)ethan-1-amine; trifluoroacetic acid (33 mg, 0.11 mmol) and potassium carbonate (34 mg, 0.25 mmol) in acetonitrile (2 mL) was heated at 150°C for 1 h using microwave irradiation. The mixture was concentrated and purified by preparative HPLC to give 6-(3-chloro-2-methylphenyl)-N4-[2-(4-methanesulfinylphenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 401.

Example 740

4-[2-({2-amino-6-[2-methyl-3-(trifluoromethyl)phenyl]pyrimidin-4-yl}amino)ethyl]benzene-1-sulfonamide

Step 1: A mixture of 1-bromo-2-methyl-3-(trifluoromethyl)benzene (100 µL, 0.64 mmol), 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (327 mg, 1.29 mmol), $PdCl_2$dppf·DCM (26 mg, 0.030 mmol) and potassium acetate (158 mg, 1.61 mmol) in 1,4-dioxane (5 mL) was heated in a sealed tube at 80°C overnight. The mixture was run through a plug of silica (EtOAc), concentrated and purified by preparative HPLC to give 4,4,5,5-tetramethyl-2-[2-methyl-3-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane.

Step 2: A mixture of 4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide (25 mg, 0.080 mmol; Intermediate 25), 4,4,5,5-tetramethyl-2-[2-methyl-3-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (26 mg, 0.090 mmol), $Pd(PPh_3)_4$ (9 mg, 0.010 mmol) and potassium carbonate (21 mg, 0.15 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 90°C overnight. The mixture was concentrated and purified by preparative HPLC to give 4-[2-({2-amino-6-[2-methyl-3-(trifluoromethyl)phenyl]pyrimidin-4-yl}amino)ethyl]benzene-

1-sulfonamide. LCMS $[M+H]^+$ 452.

Example 741

N4-[2-(4-methanesulfonylphenyl)ethyl]-6-[2-methyl-3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine

A mixture of 6-chloro-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine (25 mg, 0.080 mmol; Intermediate 33), 4,4,5,5-tetramethyl-2-[2-methyl-3-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (26 mg, 0.090 mmol) prepared in example 740, Step 1), $Pd(PPh_3)_4$ (9 mg, 0.010 mmol) and potassium carbonate (21 mg, 0.15 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 90°C overnight. The mixture was concentrated and purified by preparative HPLC to give N4-[2-(4-methanesulfonylphenyl)ethyl]-6-[2-methyl-3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 451.

Example 742

4-(3-chloro-2-methylphenyl)-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-2-amine

Step 1: To an oven-dried flask containing 4,6-dichloro-2-(methylsulfanyl)pyrimidine (390 mg, 2.0 mmol) in anhydrous THF (7.5 mL) was added TMPMgCl·LiCl (2.4 mL, 2.4 mmol; as a 1M solution in THF) at r.t. After stirring for 30 min, tert-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (469 mg, 2.1 mmol) was added and the reaction was stirred for a further 1 h at r.t. To the mixture was added 1M citric acid (7.5 mL) and EtOAc (7.5 mL) followed by vigorous stirring for 5 min. The organic layer concentrated to give tert-butyl N-{2-[4,6-dichloro-2-(methylsulfanyl)pyrimidin-5-yl]ethyl}.

Step 2: The material from Step 1 was stirred in TFA (7.5 mL) for 15 min and then concentrated. The residue was dissolved in acetonitrile (20 mL) and triethylamine (1.1 mL, 8.0 mmol) was added and the resulting mixture was heated at 80°C for 30 min. The mixture was concentrated and run through a plug of silica (EtOAc) to give 4-chloro-2-(methylsulfanyl)-5H,6H,7H-pyrrolo[2,3-d]pyrimidine.

Step 3: A mixture of 4-chloro-2-(methylsulfanyl)-5H,6H,7H-pyrrolo[2,3-d]pyrimidine (151 mg, 0.75 mmol), (3-chloro-2-methylphenyl)boronic acid (153 mg, 0.90 mmol), $Pd(PPh_3)_4$ (43 mg, 0.040 mmol) and potassium carbonate (207 mg, 1.5 mmol) in 1,4-dioxane/water (5 mL; 4:1) was heated in a sealed tube at 90°C for 1.5 h. The mixture was concentrated and purified by preparative HPLC to give 4-(3-chloro-2-methylphenyl)-2-(methylsulfanyl)-5H,6H,7H-pyrrolo[2,3-

d]pyrimidine. LCMS $[M+H]^+$ 292.

Step 4: A mixture of 4-(3-chloro-2-methylphenyl)-2-(methylsulfanyl)-5H,6H,7H-pyrrolo[2,3-d]pyrimidine; trifluoroacetic acid (70 mg, 0.17 mmol) and Oxone (318 mg, 0.52 mmol) in methanol (4 mL) and water (1.5 mL) was stirred at r.t. overnight. The mixture was concentrated and partitioned between water (15 mL) and EtOAc (30 mL). The organic layer was washed with water (15 mL) and concentrated to give 4-(3-chloro-2-methylphenyl)-2-methanesulfonyl-5H,6H,7H-pyrrolo[2,3-d]pyrimidine.

Step 5: A mixture of 4-(3-chloro-2-methylphenyl)-2-methanesulfonyl-5H,6H,7H-pyrrolo[2,3-d]pyrimidine (285 mg, 0.88 mmol), 25% aq NH_4OH (2 mL) and n-propanol (2 mL) was heated at 150°C for 1 h using microwave irradiation. The mixture was concentrated and purified by preparative HPLC to give 4-(3-chloro-2-methylphenyl)-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-2-amine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.55 - 7.65 (m, 1 H), 7.34 - 7.41 (m, 2 H), 3.73 - 3.84 (m, 2 H), 2.78 - 2.95 (m, 2 H), 2.37 (s, 3 H).

Example 743

(6R)-4-(3-Chloro-2-methylphenyl)-6-methyl-5H,6H,7H-pyrrolo[2,3-d]pyrimidin-2-amine

Prepared according to the same procedure as describe for example 742 above starting from 4,6-dichloro-2-(methylsulfanyl)pyrimidine and tert-butyl (R)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide. LCMS $[M+H]^+$ 275.

Example 744

6-(3-chloro-2-methylphenyl)-N4-(2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}ethyl)pyrimidine-2,4-diamine

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol (intermediate 55), 2-chloro-5-(trifluoromethyl)pyridine (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90 °C for 16 h. After cooling was methanol added, followed by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$ 424. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.43 - 8.53 (m, 1 H), 7.88 - 8.03 (m, 1 H), 7.52 - 7.67 (m, 1 H), 7.29 - 7.39 (m, 2 H), 6.95 - 7.00 (m, 1 H), 6.07 (s, 1 H), 4.50 - 4.69 (m, 1 H), 3.96 (t, J=5.4 Hz, 2 H), 2.38 (s, 3 H).

Example 745

6-(3-chloro-2-methylphenyl)-N4-(2-{furo[3,2-c]pyridin-4-yloxy}ethyl)pyrimidine-2,4-diamine

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol (intermediate 55), 4-chlorofuro[3,2-c]pyridine (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 110 °C for 16 h. After cooling was methanol added, followed by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$396. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.97 (d, *J*=6.0 Hz, 1 H), 7.79 (d, *J*=2.2 Hz, 1 H), 7.60 (dd, *J*=7.3, 2.2 Hz, 1 H), 7.29 - 7.38 (m, 2 H), 7.22 (dd, *J*=6.0, 0.9 Hz, 1 H), 6.92 (dd, *J*=2.2, 0.9 Hz, 1 H), 6.07 (s, 1 H), 4.69 (t, *J*=5.2 Hz, 2 H), 4.01 (t, *J*=5.4 Hz, 2 H), 2.36 (s, 3 H).

Example 746

6-(3-chloro-2-methylphenyl)-N4-{2-[(5-chloropyridin-2-yl)oxy]ethyl}pyrimidine-2,4-diamine

A mixture of 2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethanol (intermediate 55), 2,5-dichloropyridine (1.5 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 110 °C for 16 h. After cooling methanol was added followed, by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$ 390. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.09 - 8.13 (m, 1 H), 7.69 (dd, *J*=8.8, 2.8 Hz, 1 H), 7.58 - 7.63 (m, 1 H), 7.31 - 7.39 (m, 2 H), 6.83 (dd, *J*=8.8, 0.6 Hz, 1 H), 6.07 (s, 1 H), 4.51 (t, *J*=5.2 Hz, 2 H), 3.92 (t, *J*=5.4 Hz, 2 H), 2.38 (s, 3 H).

Example 747

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)benzonitrile.

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24), 4-(2-aminoethoxy)benzonitrile (1.5 equiv.) and N,N-Diisopropylethylamine (2 equiv.) in 2-propanol (0.3 mL) was heated in a sealed tube at 100°C for 30 h. Purification by column chromatography afforded the title compound (70% EtOAc in iso-Hexane). LCMS $[M+H]^+$ 380. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.75 - 7.82 (m, 2 H), 7.44 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.17 - 7.28 (m, 3 H), 7.15 (d, *J*=8.8 Hz, 2 H), 6.10 (br. s., 2 H), 5.79 (s, 1 H), 4.20 (t, *J*=5.7 Hz, 2 H), 3.60 - 3.76 (m, 2 H), 2.29 (s, 3 H),

Example 748

(Z)-4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)-N'-hydroxybenzene-1-carboximidamide

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)benzonitrile (prepared in example 747) was dissolved in DMSO (1 mL). H_2O_2 (4.0 equiv.) and 5M NaOH was added and the reaction was stirred at room temperature for 30 min. Methanol was added followed, by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$ 398. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.80 - 7.89 (m, 4 H), 7.44 (dd, *J*=7.7, 1.7 Hz, 1 H), 7.22 - 7.27 (m, 1 H), 7.20 (dd, *J*=7.7, 1.7 Hz, 2 H), 7.01 (d, *J*=8.8 Hz, 2 H), 6.10 (s, 2 H), 5.80 (s, 1 H), 4.16 (t, *J*=5.7 Hz, 2 H), 3.59 - 3.76 (m, 2 H), 2.29 (s, 3 H).

Example 749

6-(3-chloro-2-methylphenyl)-N4-{2-[4-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]ethyl}pyrimidine-2,4-diamine

A mixture of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethoxy]benzonitrile, (prepared in example 747) sodium azide (1.2 equiv), ammonium chloride (1.2 equiv.) in DMF was heated in a sealed dry tube at 130°C for 24 hours. After cooling methanol was added followed by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$ 423. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.91 - 7.99 (m, 2 H), 7.35 - 7.45 (m, 1 H), 7.17 - 7.24 (m, 2 H), 6.99 - 7.08 (m, 2 H), 5.90 (s, 1 H), 4.21 (t, *J*=5.5 Hz, 2 H), 3.73 - 3.86 (m, 2 H), 2.32 (s, 3 H)

Example 750

4-(2-(2-Amino-6-(3-chloro-2-(hydroxymethyl)phenyl)pyrimidin-4-ylamino)ethyl) benzenesulfonamide

Step 1: (3-Chloro-2-(hydroxymethyl)phenylboronic acid

The solution of 2-borono-6-chlorobenzoic acid (1.40 g, 7.0 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.60 g, 42.0 mmol) in THF (20 mL) at 0 °C. The mixture was stirred under reflux for 3 h. The solvent was removed under reduced pressure to give white solid. 1M HCl was added dropwise at 0 °C. The mixture was filtered to give the product (0.80 g). ^1H NMR

(400 MHz, DMSO-d_6): δ = 4.99 (s, 2 H), 7.41 (m, 1 H), 7.53 (m, 1 H), 7.70 (m, 1 H), 9.45 (s, 1 H) ppm.

Step 2: (2-(2-Amino-6-chloropyrimidin-4-yl)-6-chlorophenyl)methanol

To the solution of (3-Chloro-2-(hydroxymethyl)phenylboronic acid (0.80 g, 4.3 mmol), 4,6-dichloropyrimidin-2-amine (1.40 g, 8.6 mmol), and Na_2CO_3 (1.00 g, 9.5 mmol) in dioxane/H2O (32 mL/8 mL), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol, 3 mol%) was then added. The mixture was stirred for h at 90 °C. The solvent was removed under the reduced pressure. The residue was treated with DCM (10 mL x 3). The organic layer was washed with brine (10 mL). After removal of solvent under the reduced pressure, the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 5/1) to give the product (0.10 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (s, 2 H), 5.52 (m, 1 H), 6.93 (s, 1 H), 7.36 (m, 3 H), 7.55 (m, 1 H) ppm.

Step 3: 4-(2-(2-Amino-6-(3-chloro-2-(hydroxymethyl)phenyl)pyrimidin-4-ylamino)ethyl)benzenesulfonamide

To the solution of (2-(2-Amino-6-chloropyrimidin-4-yl)-6-chlorophenyl)methanol (42.7 mg, 0.16 mmol), 4-(2-aminoethyl)benzenesulfonamide (47.6 mg, 0.24 mmol) and DIPEA (41.3 mg, 0.32 mmol), the mixture was refluxed overnight. After removal the solvent under reduced pressure, the residue was purified by preparative TLC to afford the product as white solid (20.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (t, J = 6.3 Hz, 2 H), 3.82 (t, J = 6.6 Hz, 2 H), 4.75 (s, 2 H), 6.20 (s, 1 H), 7.48 (m, 4 H), 7.67 (m, 1 H), 7.86 (m, 2 H) ppm.

Example 751

(Z)-4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethoxy)-N'-hydroxybenzene-1-carboximidamide

To a solution of 4-[2-[[2-amino-6-(3-chloro-2-methyl-phenyl)pyrimidin-4-yl]amino]ethoxy]benzonitrile (intermediate 61) methanol was added the hydroxylamine HCL salt (3.0 equiv.) and N,N-Diisopropylethylamine (3.2 equiv.) and stirred at 80 °C for 90 min. The reaction mixture was cooled to 23 °C and concentrated in vacuo. Dichloromethane and water were added, the phases were separated, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude was dissolved in methanol, followed by filtration and purification by preparative LC to give the title compound. LCMS $[M+H]^+$ 413.

Example 752

6-(3-chloro-2-methylphenyl)-N4-[3-(4-methanesulfonylphenoxy)propyl]pyrimidine-2,4-diamine

A mixture of 3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propan-1-ol (intermediate 60), 1-fluoro-4-methylsulfonyl-benzene (1.1 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90°C for 1 h. After cooling was methanol added to the solution, followed by filtration and purification by preparative LC to furnish the title compound. LCMS $[M+H]^+$ 447. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.85 - 7.91 (m, 2 H), 7.60 (dd, *J*=7.4, 2.1 Hz, 1 H), 7.34 (d, *J*=5.7 Hz, 2 H), 7.10 - 7.18 (m, 2 H), 6.04 (s, 1 H), 4.22 (t, *J*=6.0 Hz, 2 H), 3.75 (t, *J*=6.6 Hz, 2 H), 3.08 (s, 3 H), 2.37 (s, 3 H), 2.18 (quin, *J*=6.3 Hz, 2 H)

Example 753

2-(3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propoxy)pyrimidine-4-carboxamide

A mixture of 3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propan-1-ol (intermediate 60), 2-chloropyrimidine-4-carboxamide (1.1 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90°C for 2 h. After cooling was methanol added to the solution, followed by filtration and purification by preparative LC to furnish the title compound. LCMS $[M+H]^+$ 414. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.79 (d, *J*=5.1 Hz, 1 H), 7.69 (s, 1 H), 7.55 - 7.63 (m, 1 H), 7.30 - 7.41 (m, 3 H), 6.04 (s, 1 H), 4.59 (t, *J*=6.0 Hz, 2 H), 3.76 (t, *J*=6.8 Hz, 2 H), 2.18 (quin, *J*=6.3 Hz, 3 H).

Example 754

6-(3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propoxy)pyridine-3-carboxamide.

A mixture of 3-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propan-1-ol (intermediate 60), 6-chloropyridine-3-carboxamide (1.1 equiv.) and Cs_2CO_3 (2.0 equiv.) in DMSO was heated in a sealed tube at 90°C for 2 h. After cooling was methanol added to the solution, followed by filtration and purification by preparative LC to furnish the title compound. LCMS $[M+H]^+$ 413. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 8.67 (dd, *J*=2.5, 0.6 Hz, 1 H), 8.13 (dd, *J*=8.8, 2.5 Hz, 1 H), 7.58 - 7.63 (m, 1 H), 7.29 - 7.40 (m, 2 H), 6.86 (dd, *J*=8.8, 0.6 Hz, 1 H),

6.03 (s, 1 H), 4.48 (t, *J*=6.2 Hz, 2 H), 3.72 (t, *J*=6.6 Hz, 2 H), 2.37 (s, 3 H), 2.15 (quin, *J*=6.4 Hz, 2 H).

Example 755

6-(3-chloro-2-methylphenyl)-N4-{2-[4-(morpholine-4-sulfonyl)phenyl]ethyl}pyrimidine-2,4-diamine

Morpholine (6 equiv.) and 4-(2-acetamidoethyl)benzene-1-sulfonyl chloride (intermediate 62) (1 equiv.) were heated neat at 70°C for 30 min. 2.5 M NaOH (26 equiv.) was added and the reaction was heated in the micro wave oven for 15 min at 150°C. The mixture was extracted with DCM and the organic phase was dried over $MgSO_4$ and removed in vacuo. The crude product was dissolved in MeOH and 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24) (1 equiv.) was added. The solvent was removed and the mixture was melted for 15 min at 160°C. The crude material was dissolved in MeOH and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 488. ^1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.29 (3 H, s) 2.78 - 2.88 (4 H, m) 2.96 (2 H, t, *J*=7.19 Hz) 3.45 - 3.59 (2 H, m) 3.59 - 3.67 (4 H, m) 5.74 (1H, s) 6.06 (2 H, br. s.) 7.07 (1 H, br. s.) 7.17 - 7.27 (2 H, m) 7.40 - 7.47 (1 H, m) 7.53 - 7.59 (2 H, m) 7.63 - 7.70 (2 H, m)

Example 756

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-(2-methoxyethyl)benzene-1-sulfonamide

2-Methoxyethan-1-amine (6 equiv.) and 4-(2-acetamidoethyl)benzene-1-sulfonyl chloride (intermediate 62) (1 equiv.) were heated neat at 70°C for 30 min. 2,5M NaOH (26 equiv.) was added and the reaction was heated in the micro for 15 min at 150°C. 12M HCl (26 equiv.) was added and the solvent was removed in vacuo. MeOH was added and NaCl was removed by filtration. 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24) (1 equiv.) was added and the solvent was evaporated at 80°C. The crude material was melted at 160°C for 30 min. The crude material was dissolved in MeOH and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 476.

Example 757

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-(oxetan-3-yl)benzene-1-sulfonamide

Oxetan-3-amine (6 equiv.) and 4-(2-acetamidoethyl)benzene-1-sulfonyl chloride intermediate 62 (1 equiv.) were heated neat at 70°C for 30 min. 2,5M NaOH (26 equiv.) was added and the reaction was heated in the micro for 15 min at 150°C. 12M HCl (26 equiv.) was added and the solvent was removed in vacuo. MeOH was added and NaCl was removed by filtration. 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24) (1 equiv.) was added and the solvent was evaporated at 80°C. The crude material was melted at 160°C for 30 min. The crude material was dissolved in MeOH and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 474.

Example 758

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-(oxan-4-yl)benzene-1-sulfonamide

oxan-4-amine (6 equiv.) and 4-(2-acetamidoethyl)benzene-1-sulfonyl chloride intermediate 62 (1 equiv.) were heated neat at 70°C for 30 min. 2,5M NaOH (26 equiv.) was added and the reaction was heated in the micro for 15 min at 150°C. 12M HCl (26 equiv.) was added and the solvent was removed in vacuo. MeOH was added and NaCl was removed by filtration. 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (intermediate 24) (1 equiv.) was added and the solvent was evaporated at 80°C. The crude material was melted at 160°C for 30 min. The crude material was dissolved in MeOH and purified by preparative LC to afford the title compound. LCMS $[M+H]^+$ 502.

Example 759

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N-methyl-N-(prop-2-yn-1-yl)benzamide.

Step 1 sodium 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzoate.

Methyl 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzoate (prepared in example 710) (1 eq), MeOH and 5M NaOH (1.1 eq) were heated in a sealed tube for 8 hours at 115°C. The title compound was isolated by removing the solvent *in vacuo*. LCMS $[M+H]^+$ 383.

Step 2 TBTU (1.5 eq) was added to a stirred mixture of sodium 4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzoate (1 eq),

methyl(prop-2-yn-1-yl)amine (3 eq), Hunigs (5 eq) and dry DMF. The mixture was stirred at r.t. in a sealed tube for 4 hours. The mixture was purified by preparative LC to give the title compound. LCMS [M+H]+ 434 1H NMR (400 MHz, DMSO-d6) d ppm 2.26 - 2.31 (3 H, m) 2.88 (1 H, t, J=7.35 Hz) 2.97 (3 H, br. s.) 3.23 - 3.40 (1 H, m) 3.51 (2 H, br. s.) 3.95 - 4.41 (2 H, m) 5.74 (1 H, s) 6.06 (2 H, br. s.) 7.08 (1 H, br. s.) 7.18 - 7.28 (2 H, m) 7.32 - 7.40 (4 H, m) 7.44 (1 H, dd, J=7.58, 1.74 Hz)

Example 760

6-(3-chloro-2-methylphenyl)-N4-[2-(4-ethynylphenyl)ethyl]pyrimidine-2,4-diamine

Step 1: N4-[2-(4-bromophenyl)ethyl]-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine

N_2 was bubbled through a mixture of N4-[2-(4-bromophenyl)ethyl]-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine, prepared in example 736, (1 eq), Et_3N (1 eq), PPh3 (0.2 eq), CuI (0.05 eq) and DMF for 3 min. $PdCl_2(PPh_3)_2$ (0.05 eq) and ethynyltrimethylsilane (2 eq) was added and the reaction was heated in a sealed tube for 1 hour at 120°C. The mixture was cold to r.t. and 1M tetrabutyl ammonium fluoride in THF (5 eq) was added. The reaction was stirred for 1 hour at r.t. MeOH was added followed by filtration and purified by preparative LC to give the title compound. LCMS $[M+H]^+$ 363. 1H NMR (400 MHz, DMSO-d6) d ppm 2.29 (3 H, s) 2.84 (2 H, t, J=7.27 Hz) 3.48 (2 H, br. s.) 4.13 (1 H, s) 5.72 (1 H, s) 6.05 (2 H, br. s.) 7.03 (1 H, br. s.) 7.17 - 7.31 (4 H, m) 7.38 - 7.46 (3 H, m)

Example 761

6-(2-(2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)ethoxy)pyridine-3-sulfonamide

Step 1: 6-Chloropyridine-3-sulfonamide

$SOCl_2$ (24mL) was added to water (145mL) containing CuCl (87 mg) at 0 °C over a period of 30 min. The solution was then stirred at RT overnight.

3-amino-6-chloropyridine (10.0 g, 77.8 mmol) was added with stirring to conc. HCl (80 mL) portionwise. The mixture was stirred until all solid was dissolved. At -5 °C a solution of $NaNO_2$ (5.9 g, 85.5 mmol, in 24 mL H_2O) was added dropwise while the temperature was kept between -5 °C and 0 °C. The resulting mixture was stirred for 30 min after completion of the addition and then added dropwise into the aqueous solution of $SOCl_2$. The temperature was kept below 0 °C during the addition. After the addition the mixture was stirred for 1h below 0 °C and then

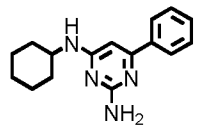
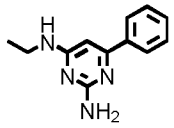
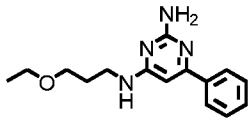
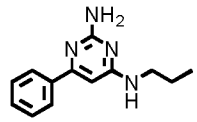
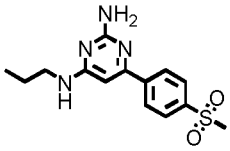
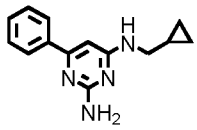
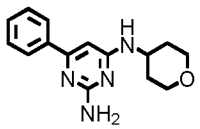
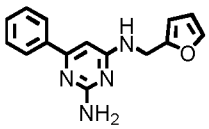
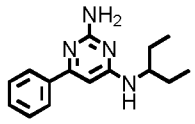
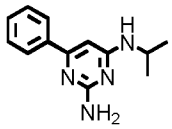
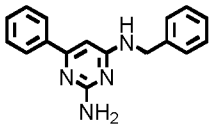
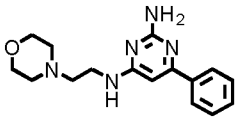
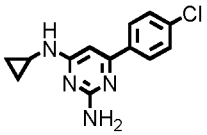
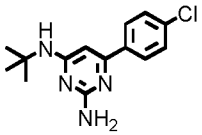
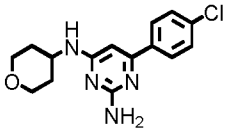
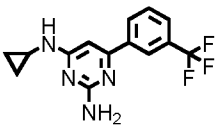
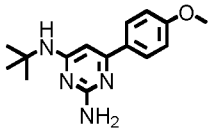
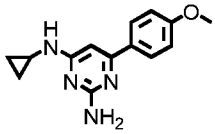
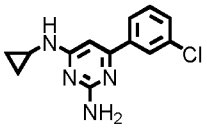
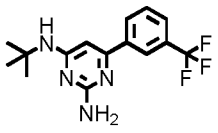
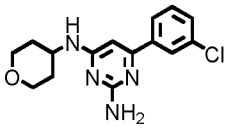
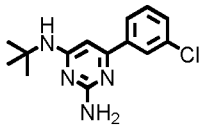
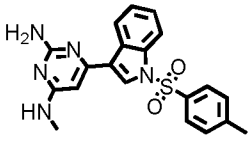
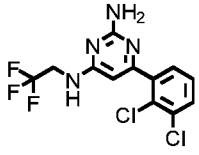
filtered. The cake was washed with ice-cold water (5 mL). A yellow solid was obtained as crude product (16 g), which was added with stirring into 50% aqueous ammonia (80 mL) portionwise at 10 °C. The mixture was then stirred at RT for 30 min, then was extracted with EA (150 mL x 1,50 mL x 2), the combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded the product ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.73 (s, 2 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 8.22 (m, 1 H), 8.80 (d, *J* = 2.0 Hz, 1 H) ppm.

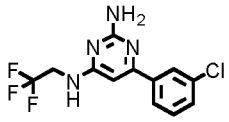
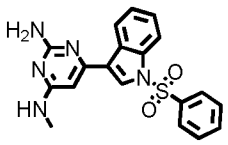
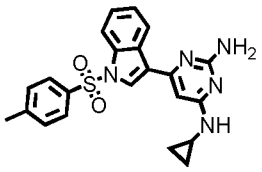
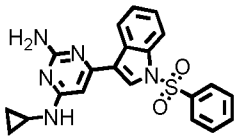
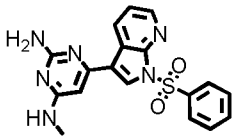
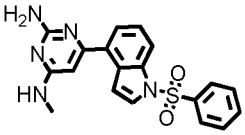
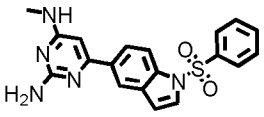
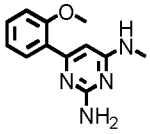
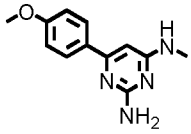
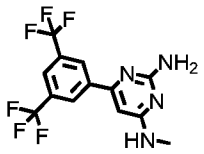
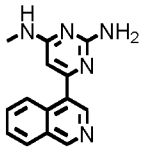
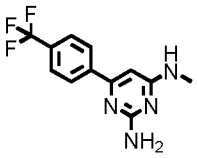
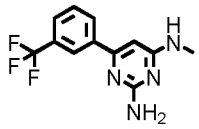
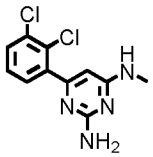
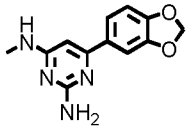
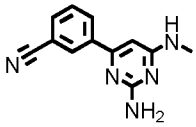
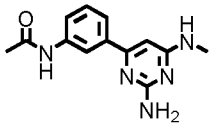
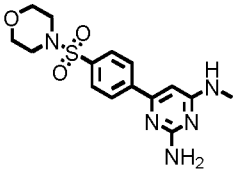
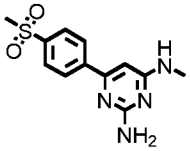
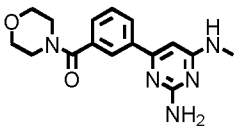
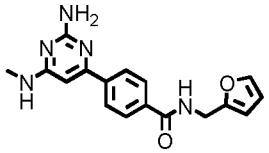
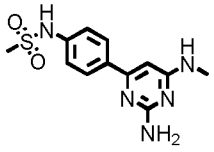
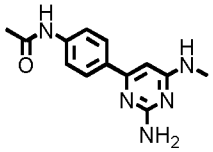
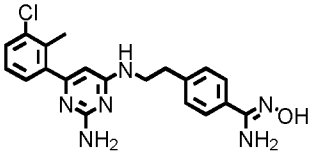
Step 2: 6-(2-Aminoethoxy)pyridine-3-sulfonamide

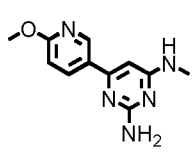
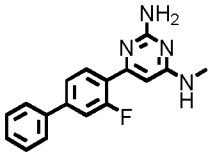
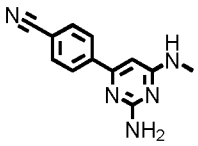
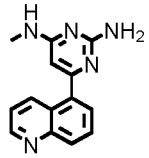
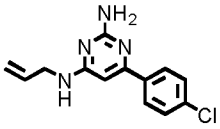
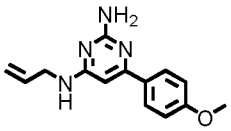
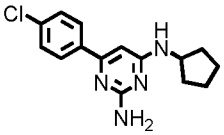
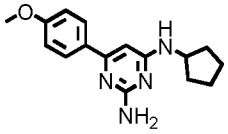
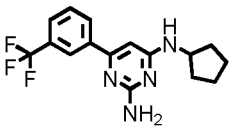
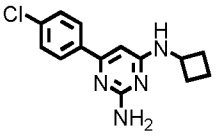
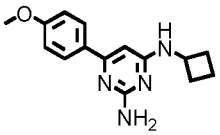
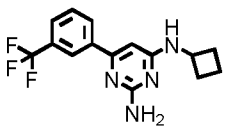
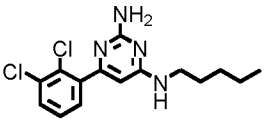
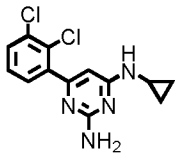
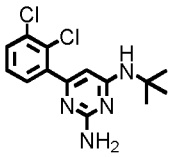
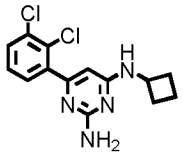
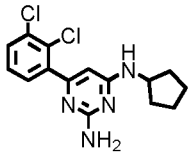
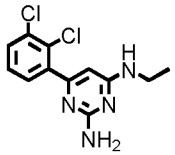
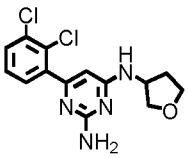
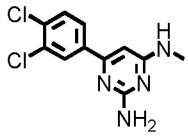
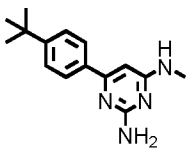
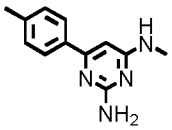
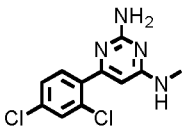
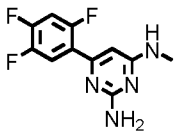
To the solution of 2-aminoethanol (2.4 g, 38.9 mmol) in dioxane (60 mL) was added NaH (60 %, 1.40 g, 35.1 mmol) in portions at 10 °C. After 30 min stirring at RT, 6-Chloropyridine-3-sulfonamide (1.50 g, 7.8 mmol) was added. The mixture was stirred for 30 min under reflux. After cooling to RT, the reaction was quenched by adding H_2O (0.5 mL). The organic layer was separated and dried over Na_2SO_4. After removal of solvent under reduced pressure, the residue was purified by column chromatography. Recrystallization from MeCN afforded a yellow the product (0.42 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.89 (t, *J* = 6.0 Hz, 2 H), 4.27 (t, *J* = 6.0 Hz, 2 H), 4.62 (br, 2 H), 6.99 (m, 1 H), 8.05 (m, 1 H), 8.55 (m, 1 H) ppm.

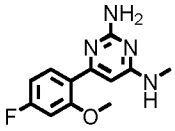
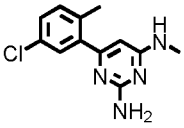
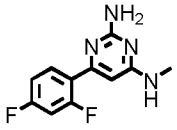
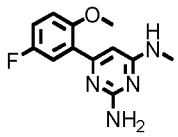
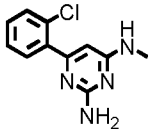
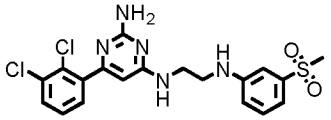
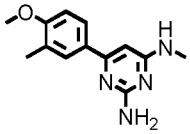
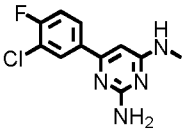
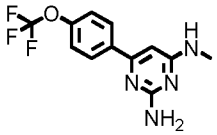
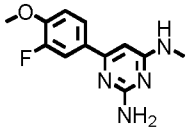
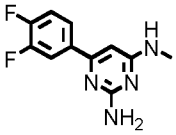
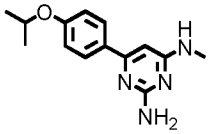
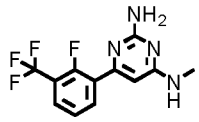
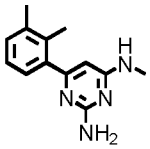
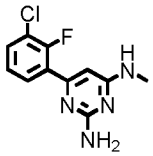
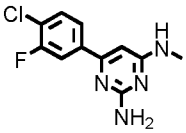
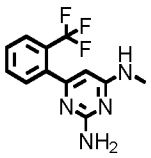
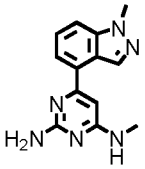
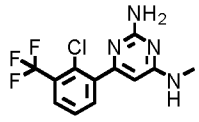
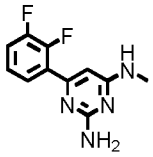
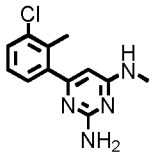
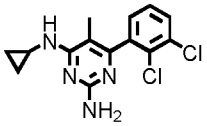
Step 3: 6-(2-(2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-ylamino)ethoxy)pyridine-3-sulfonamide

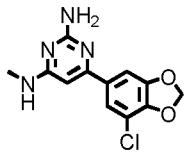
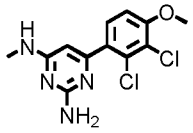
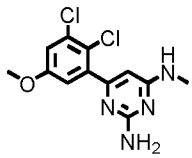
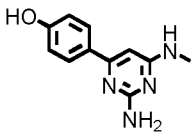
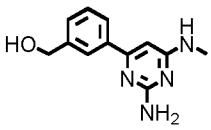
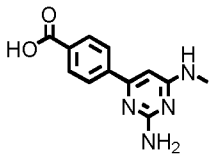
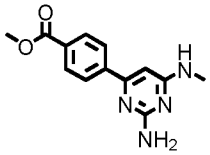
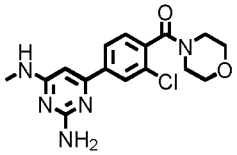
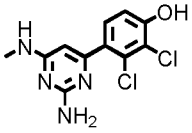
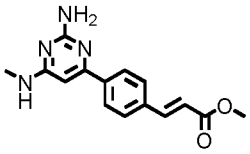
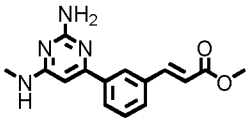
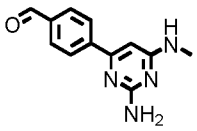
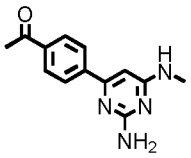
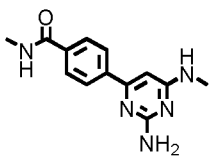
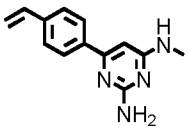
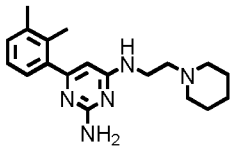
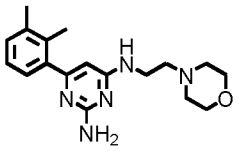
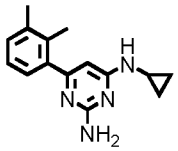
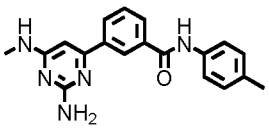
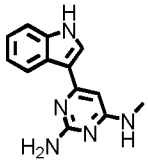
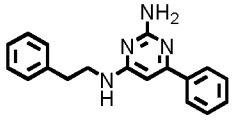
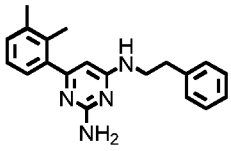
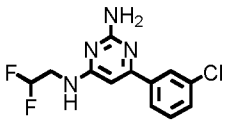
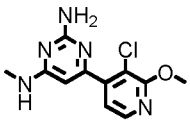
The mixture of 6-(2-Aminoethoxy)pyridine-3-sulfonamide prepared in step 2 (0.42 g, 1.9 mmol), and intermediate 24 (0.98 g, 3.8 mmol) and TEA (0.59 g, 5.8 mmol) in *i*-PrOH (15 mL) was stirred at 95 °C overnight. After cooling to RT and removal of solvent under reduced pressure, the residue was purified by column chromatography (to afford a white solid which was purified by prep HPLC to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.29 (s, 2 H), 3.67 (s, 2 H), 4.46 (t, *J* = 5.6 Hz, 2 H), 5.79 (s, 1 H), 6.09 (s, 2 H), 7.01 (d, *J* = 8.8 Hz, 1 H), 7.24 (m, 3 H), 7.44 (m, 1 H), 8.07 (m, 1 H), 8.56 (d, *J* = 2.4 Hz, 1 H) ppm.

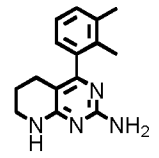
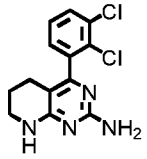
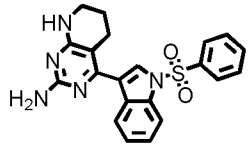
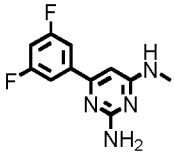
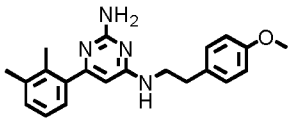
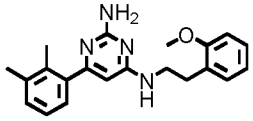
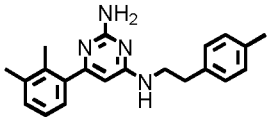
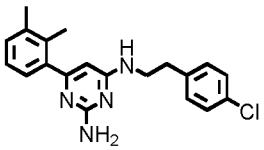
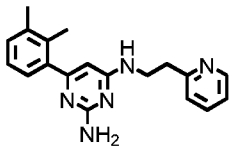
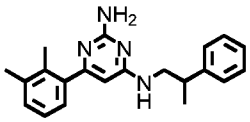
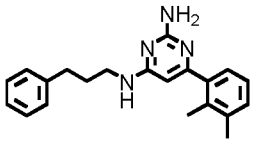
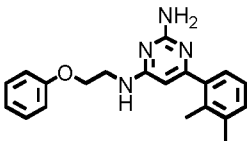
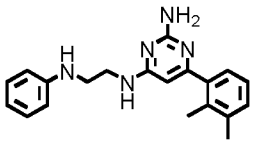
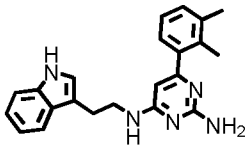
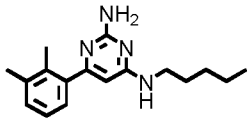
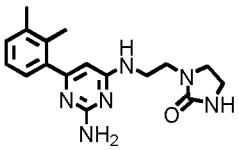
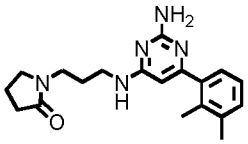
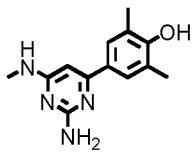
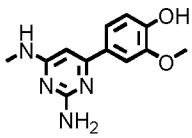
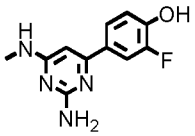
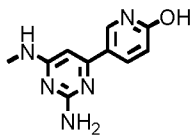
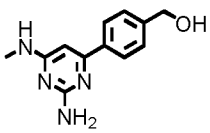
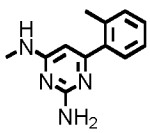
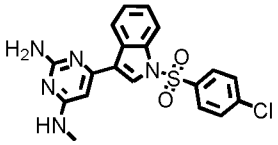
 Example 1	 Example 2	 Example 3
 Example 4	 Example 5	 Example 6
 Example 7	 Example 8	 Example 9
 Example 10	 Example 11	 Example 12
 Example 13	 Example 14	 Example 15
 Example 16	 Example 17	 Example 18
 Example 19	 Example 20	 Example 21
 Example 22	 Example 23	 Example 24

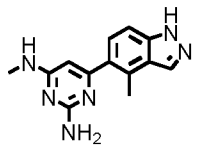
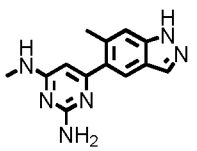
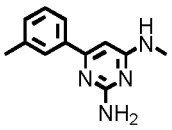
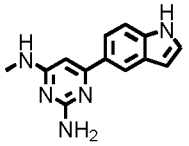
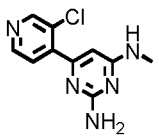
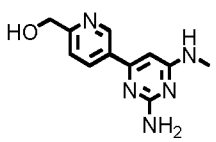
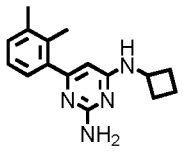
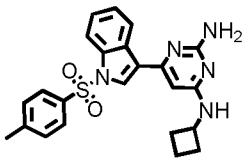
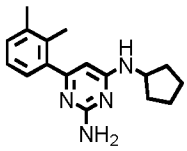
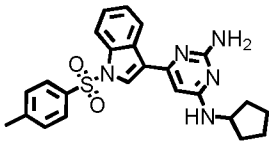
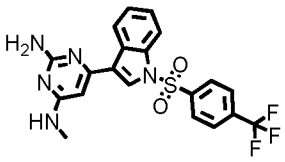
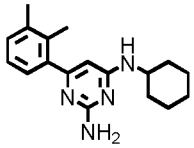
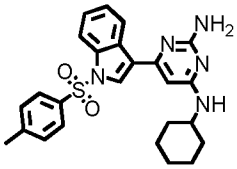
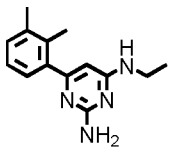
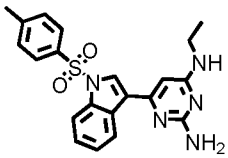
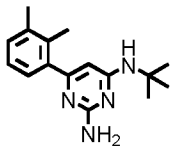
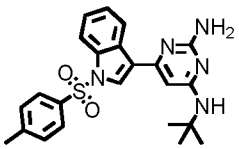
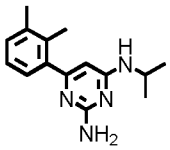
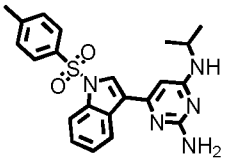
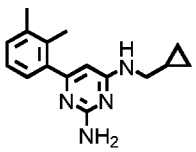
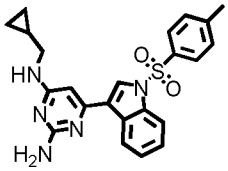
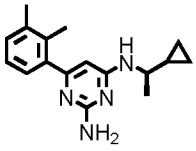
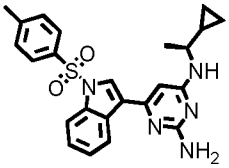
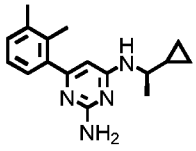
 Example 25	 Example 26	 Example 27
 Example 28	 Example 29	 Example 30
 Example 31	 Example 32	 Example 33
 Example 34	 Example 35	 Example 36
 Example 37	 Example 38	 Example 39
 Example 40	 Example 41	 Example 42
 Example 43	 Example 44	 Example 45
 Example 46	 Example 47	 Example 48

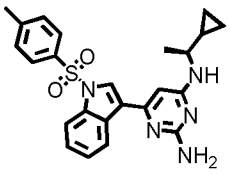
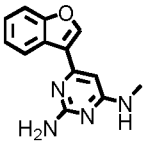
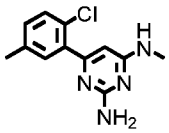
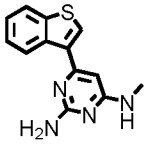
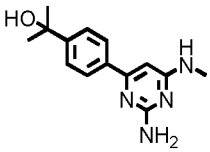
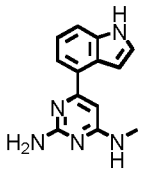
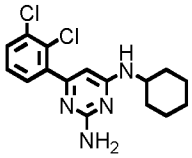
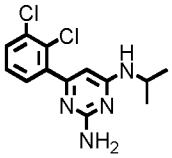
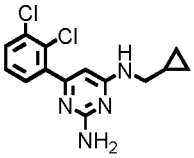
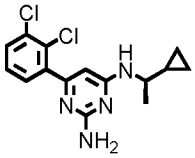
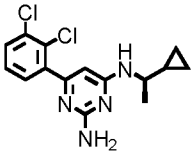
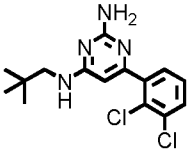
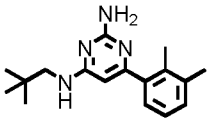
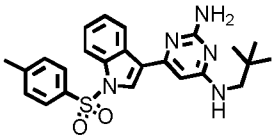
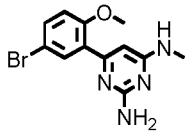
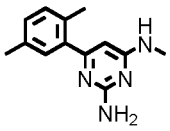
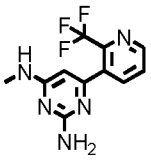
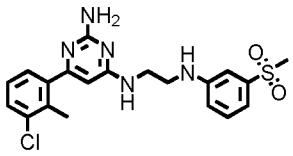
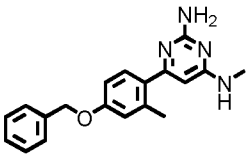
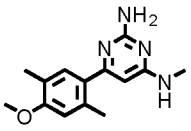
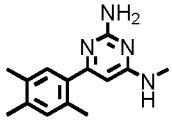
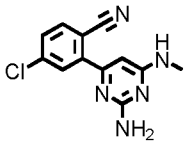
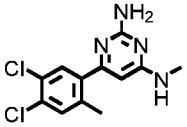
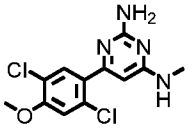
 Example 49	 Example 50	 Example 51
 Example 52	 Example 53	 Example 54
 Example 55	 Example 56	 Example 57
 Example 58	 Example 59	 Example 60
 Example 61	 Example 62	 Example 63
 Example 64	 Example 65	 Example 66
 Example 67	 Example 68	 Example 69
 Example 70	 Example 71	 Example 72

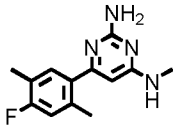
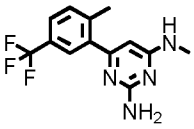
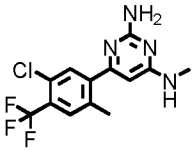
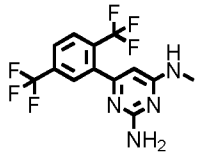
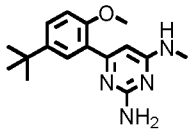
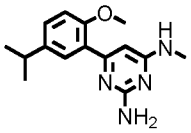
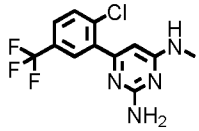
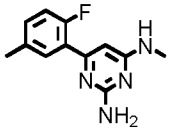
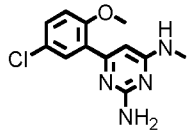
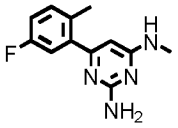
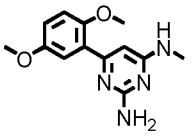
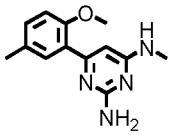
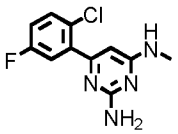
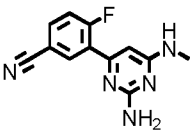
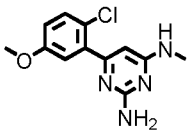
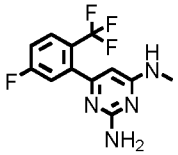
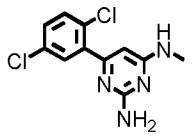
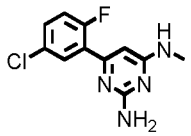
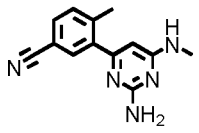
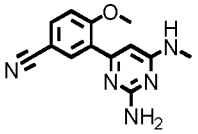
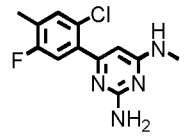
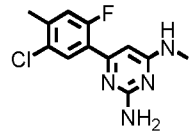
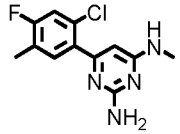
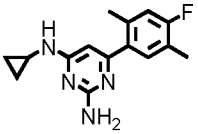
 Example 73	 Example 74	 Example 75
 Example 76	 Example 77	 Example 78
 Example 79	 Example 80	 Example 81
 Example 82	 Example 83	 Example 84
 Example 85	 Example 86	 Example 87
 Example 88	 Example 89	 Example 90
 Example 91	 Example 92	 Example 93
 Example 94	 Example 95	 Example 96

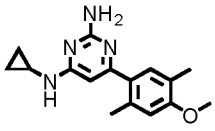
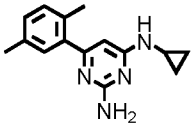
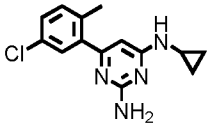
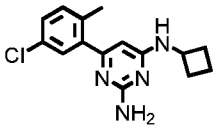
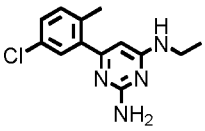
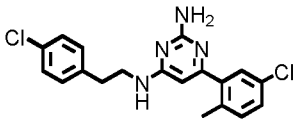
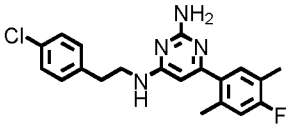
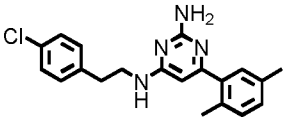
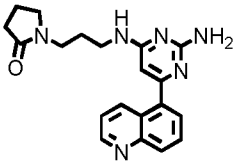
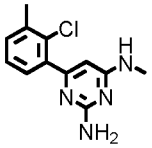
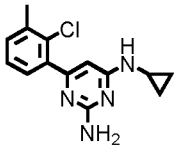
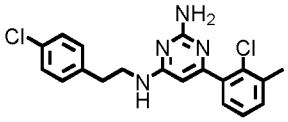
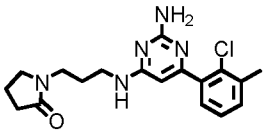
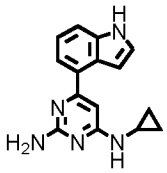
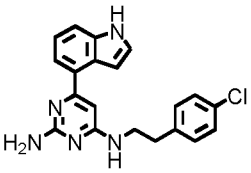
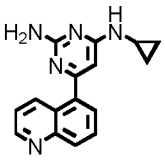
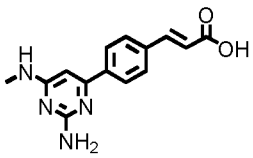
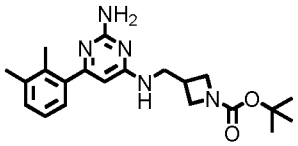
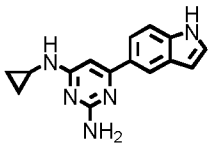
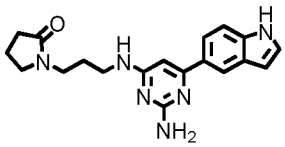
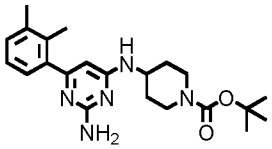
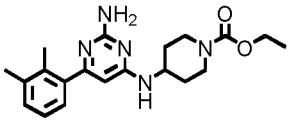
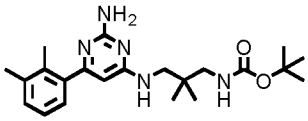
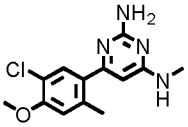
 Example 97	 Example 98	 Example 99
 Example 100	 Example 101	 Example 102
 Example 103	 Example 104	 Example 105
 Example 106	 Example 107	 Example 108
 Example 109	 Example 110	 Example 111
 Example 112	 Example 113	 Example 114
 Example 115	 Example 116	 Example 117
 Example 118	 Example 119	 Example 120

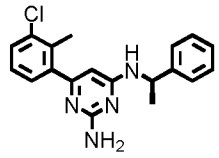
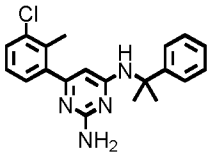
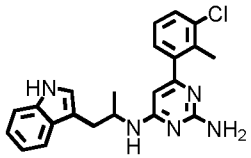
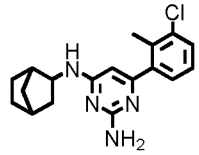
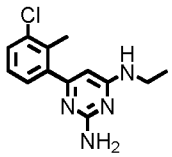
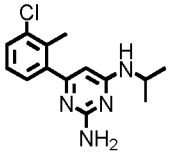
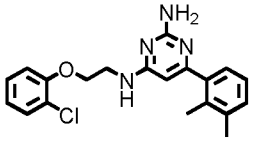
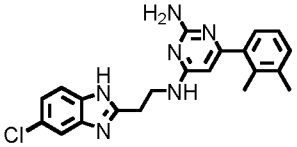
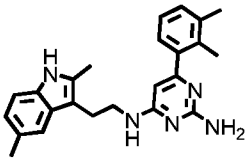
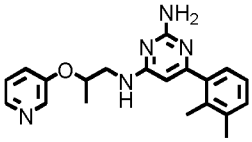
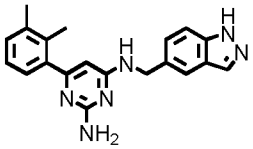
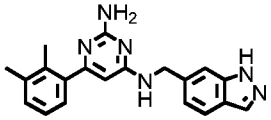
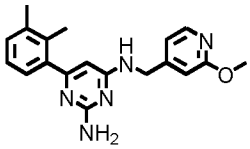
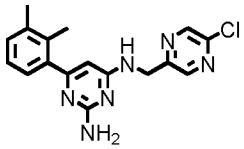
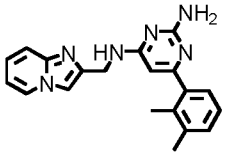
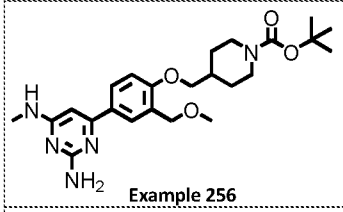
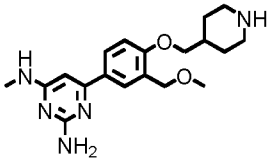
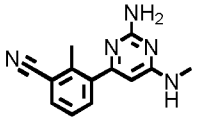
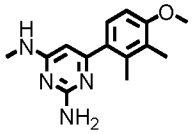
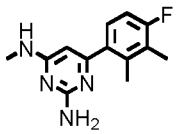
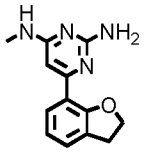
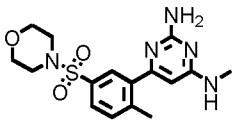
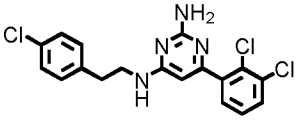
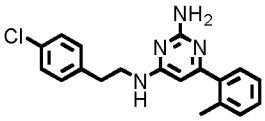
 Example 121	 Example 122	 Example 123
 Example 124	 Example 125	 Example 126
 Example 127	 Example 128	 Example 129
 Example 130	 Example 131	 Example 132
 Example 133	 Example 134	 Example 135
 Example 136	 Example 137	 Example 138
 Example 139	 Example 140	 Example 141
 Example 142	 Example 143	 Example 144

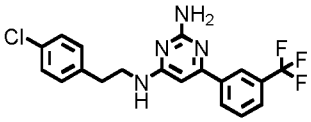
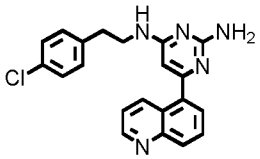
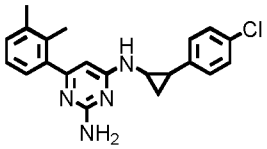
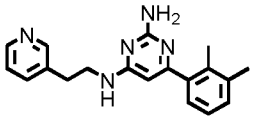
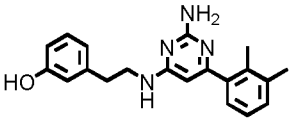
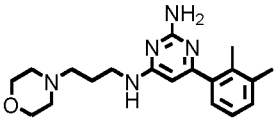
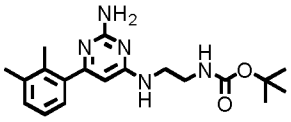
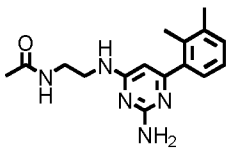
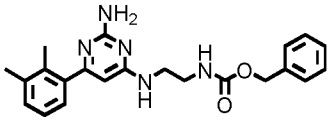
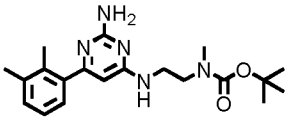
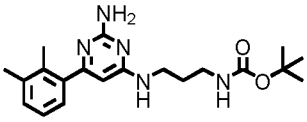
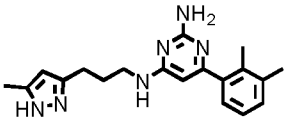
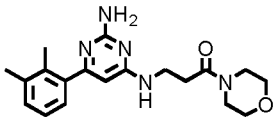
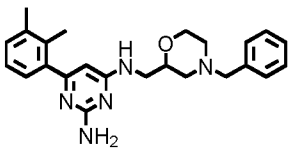
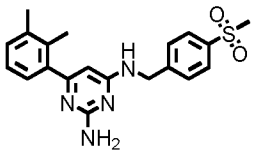
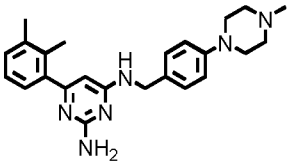
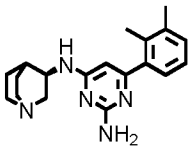
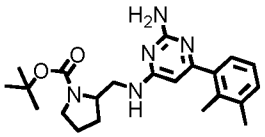
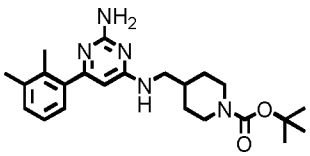
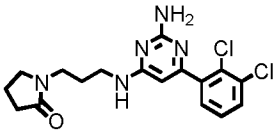
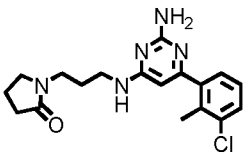
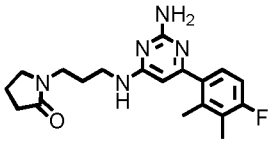
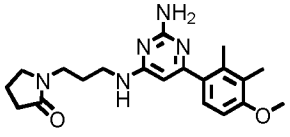
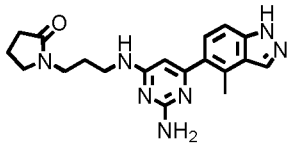
 Example 145	 Example 146	 Example 147
 Example 148	 Example 149	 Example 150
 Example 151	 Example 152	 Example 153
 Example 154	 Example 155	 Example 156
 Example 157	 Example 158	 Example 159
 Example 160	 Example 161	 Example 162
 Example 163	 Example 164	 Example 165
 Example 166	 Example 167	 Example 168

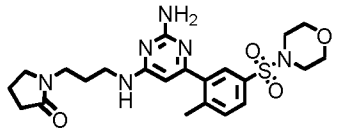
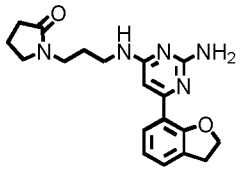
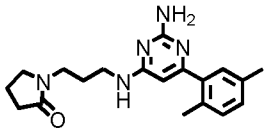
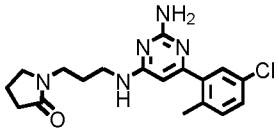
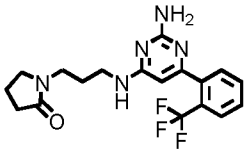
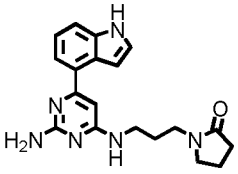
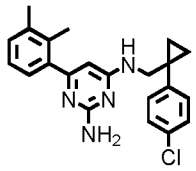
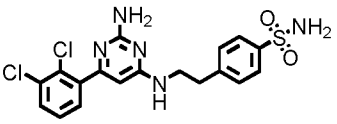
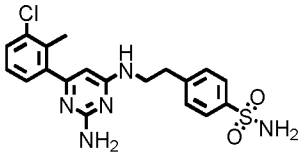
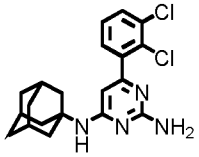
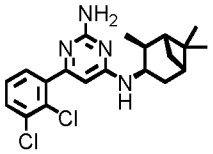
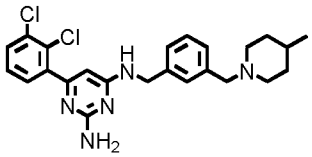
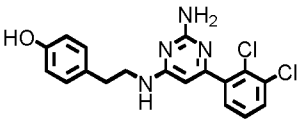
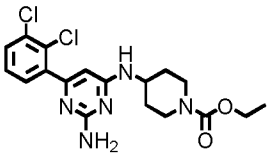
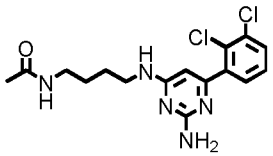
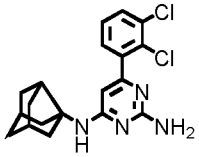
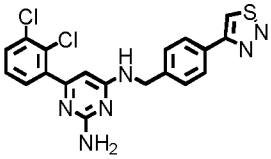
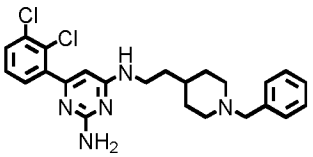
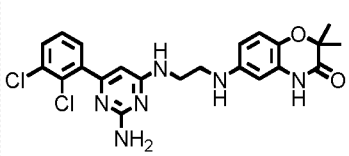
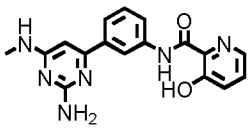
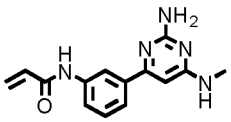
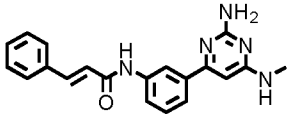
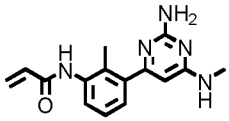
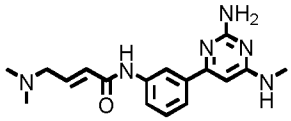
 Example 169	 Example 170	 Example 171
 Example 172	 Example 173	 Example 174
 Example 175	 Example 176	 Example 177
 Example 178	 Example 179	 Example 180
 Example 181	 Example 182	 Example 183
 Example 184	 Example 185	 Example 186
 Example 187	 Example 188	 Example 189
 Example 190	 Example 191	 Example 192

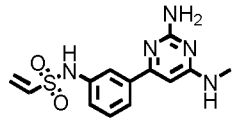
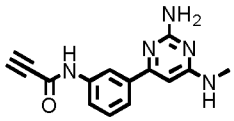
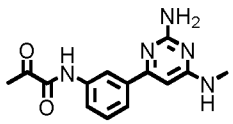
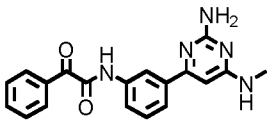
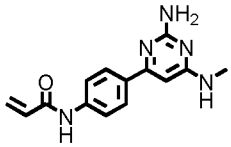
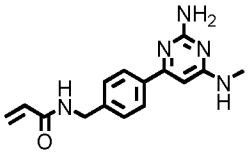
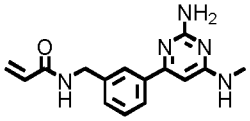
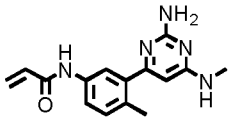
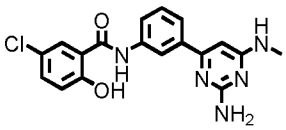
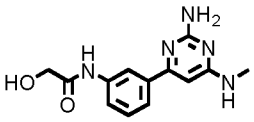
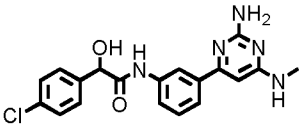
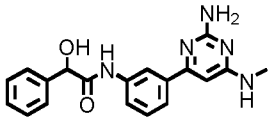
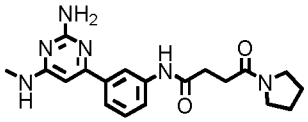
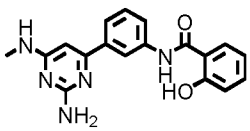
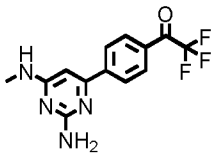
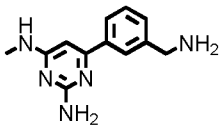
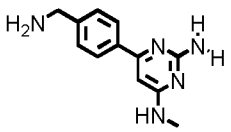
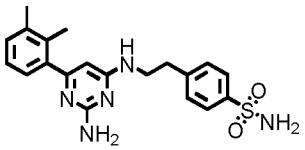
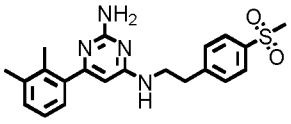
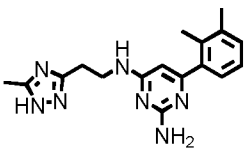
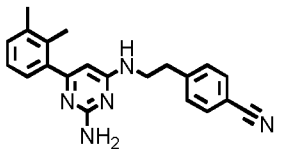
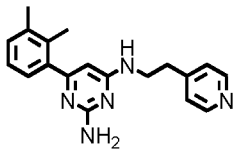
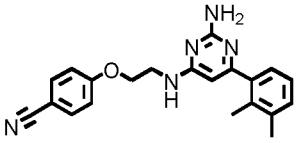
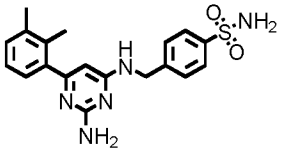
 Example 193	 Example 194	 Example 195
 Example 196	 Example 197	 Example 198
 Example 199	 Example 200	 Example 201
 Example 202	 Example 203	 Example 204
 Example 205	 Example 206	 Example 207
 Example 208	 Example 209	 Example 210
 Example 211	 Example 212	 Example 213
 Example 214	 Example 215	 Example 216

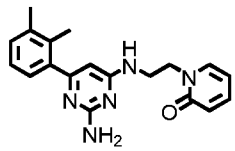
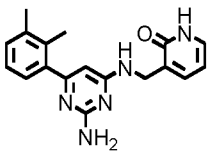
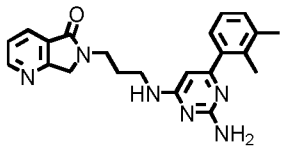
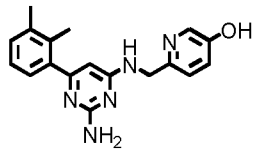
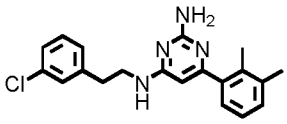
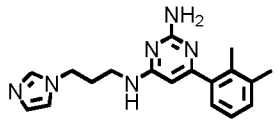
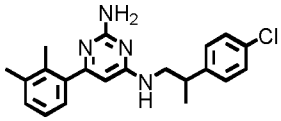
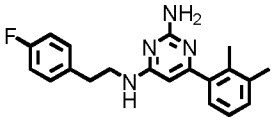
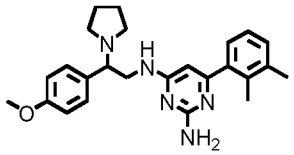
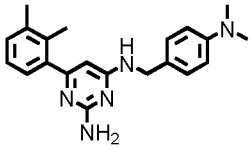
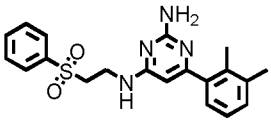
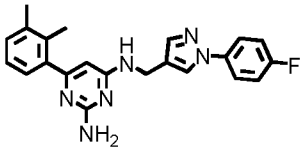
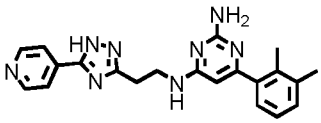
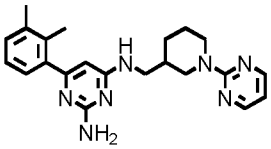
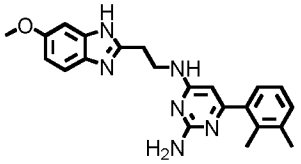
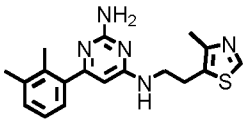
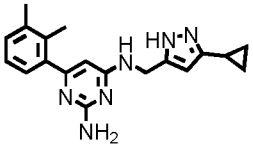
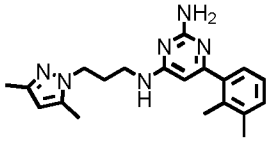
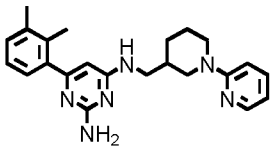
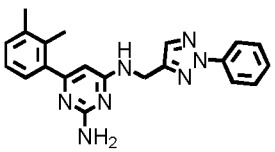
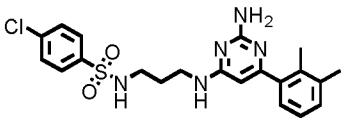
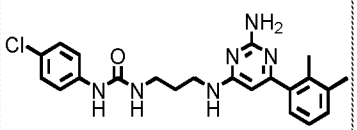
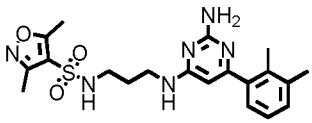
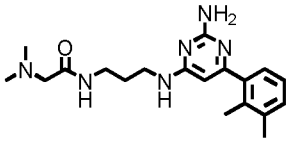
 Example 217	 Example 218	 Example 219
 Example 220	 Example 221	 Example 222
 Example 223	 Example 224	 Example 225
 Example 226	 Example 227	 Example 228
 Example 229	 Example 230	 Example 231
 Example 232	 Example 233	 Example 234
 Example 235	 Example 236	 Example 237
 Example 238	 Example 239	 Example 240

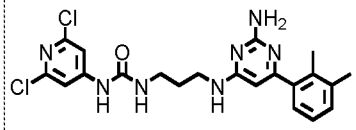
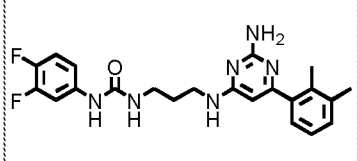
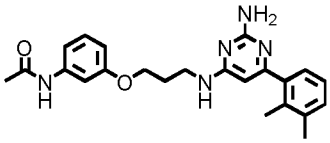
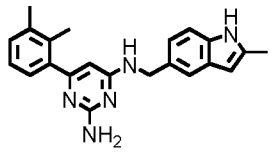
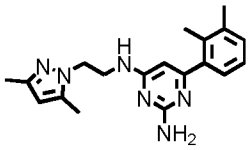
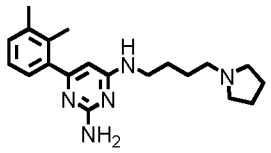
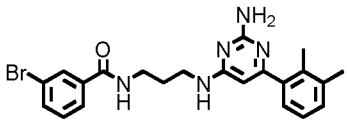
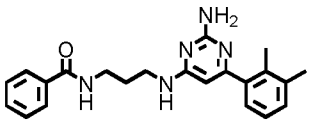
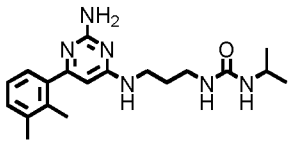
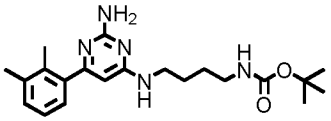
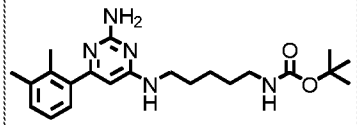
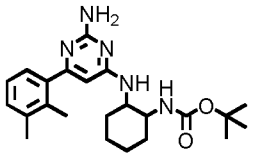
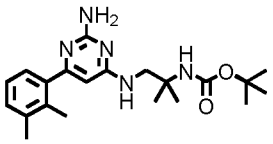
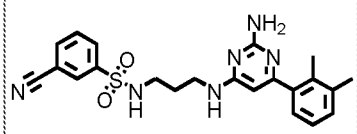
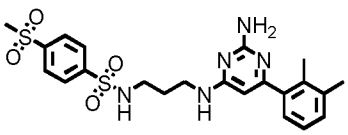
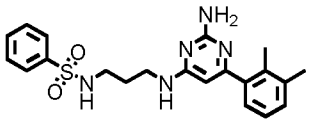
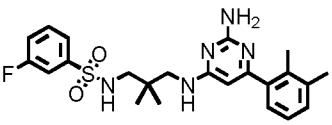
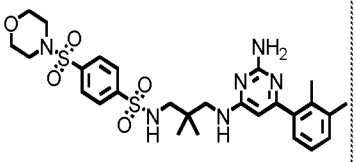
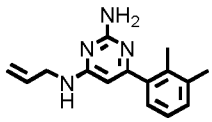
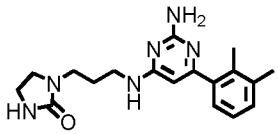
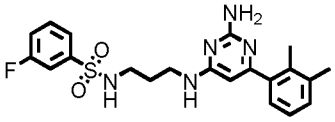
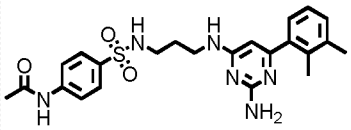
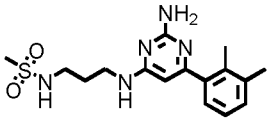
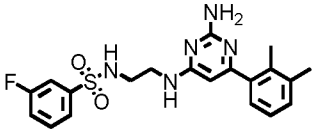
 Example 241	 Example 242	 Example 243
 Example 244	 Example 245	 Example 246
 Example 247	 Example 248	 Example 249
 Example 250	 Example 251	 Example 252
 Example 253	 Example 254	 Example 255
 Example 256	 Example 257	 Example 258
 Example 259	 Example 260	 Example 261
 Example 262	 Example 263	 Example 264

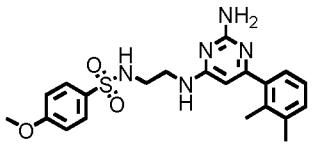
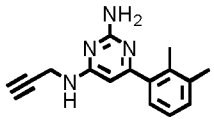
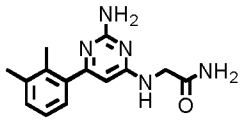
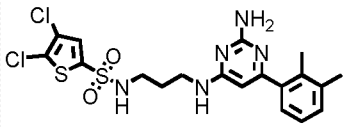
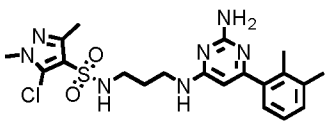
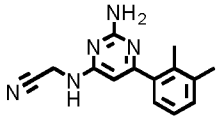
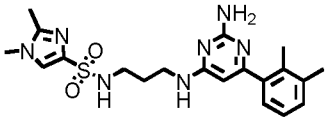
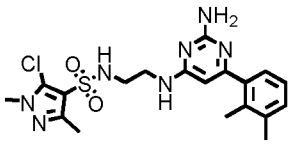
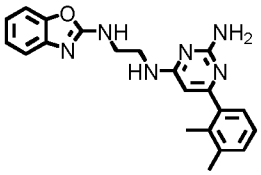
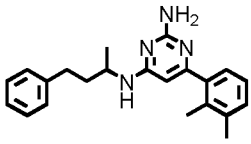
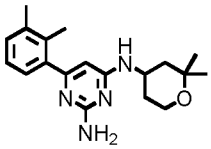
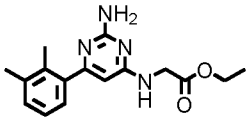
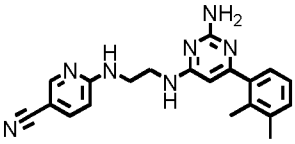
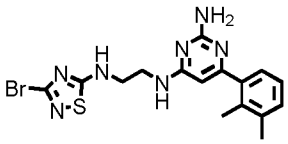
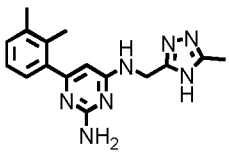
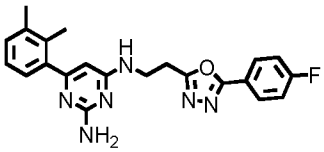
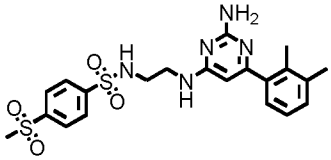
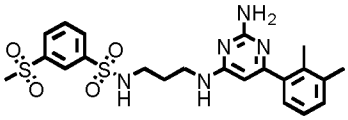
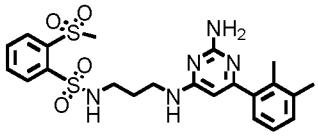
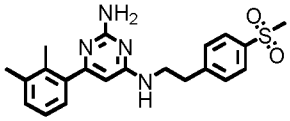
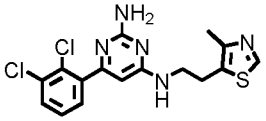
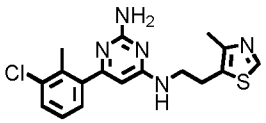
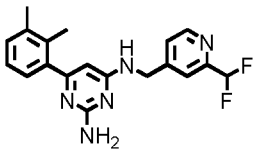
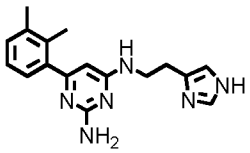
 Example 265	 Example 266	 Example 267
 Example 268	 Example 269	 Example 270
 Example 271	 Example 272	 Example 273
 Example 274	 Example 275	 Example 276
 Example 277	 Example 278	 Example 279
 Example 280	 Example 281	 Example 282
 Example 283	 Example 284	 Example 285
 Example 286	 Example 287	 Example 288

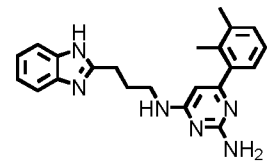
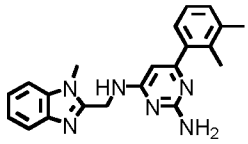
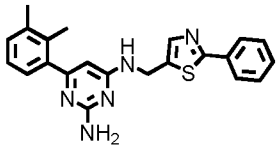
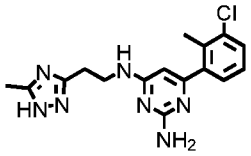
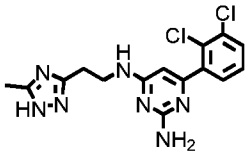
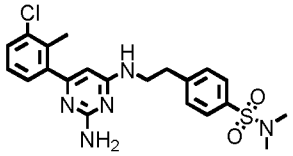
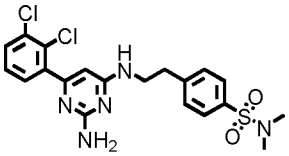
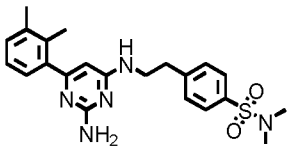
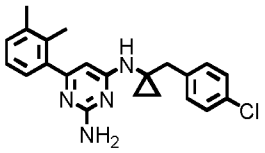
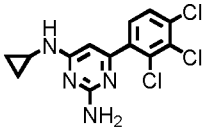
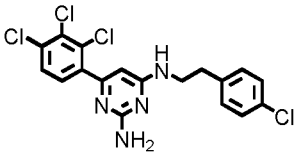
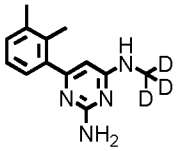
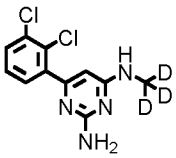
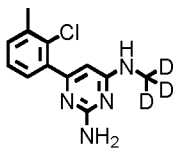
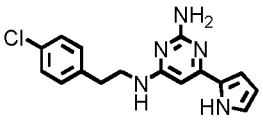
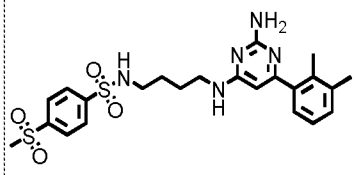
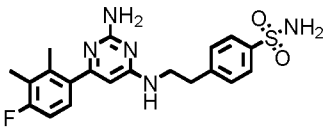
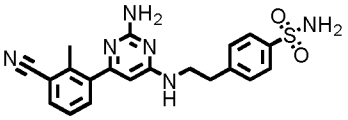
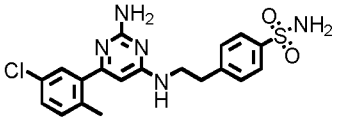
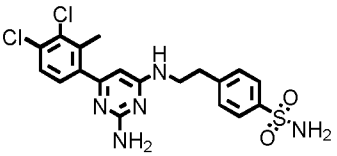
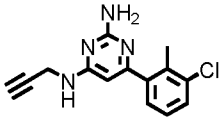
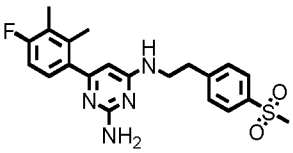
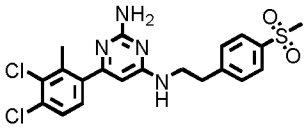
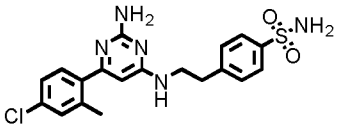
 Example 289	 Example 290	 Example 291
 Example 292	 Example 293	 Example 294
 Example 295	 Example 296	 Example 297
 Example 298	 Example 299	 Example 300
 Example 301	 Example 302	 Example 303
 Example 304	 Example 305	 Example 306
 Example 307	 Example 308	 Example 309
 Example 310	 Example 311	 Example 312

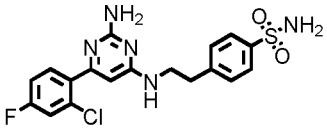
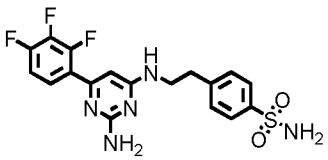
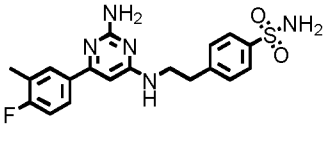
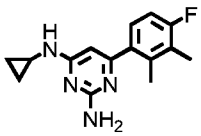
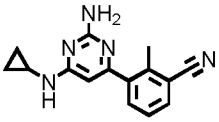
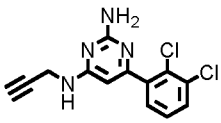
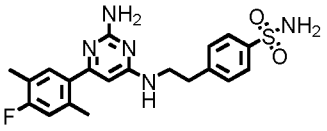
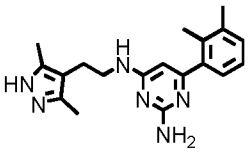
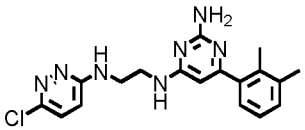
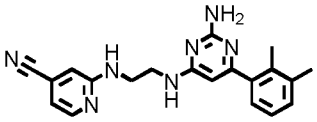
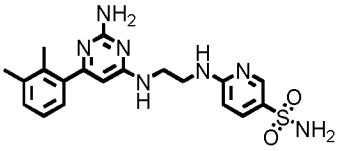
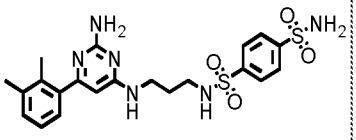
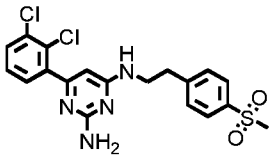
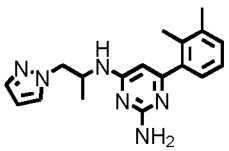
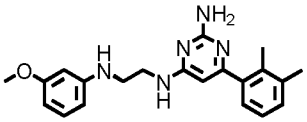
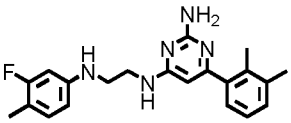
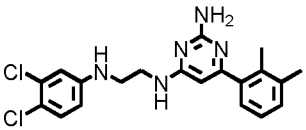
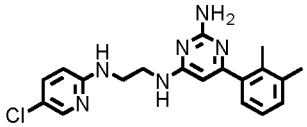
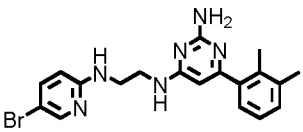
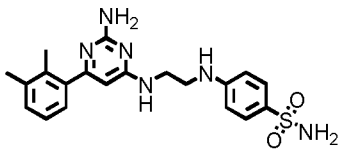
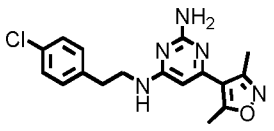
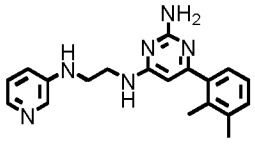
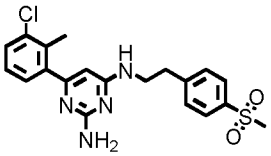
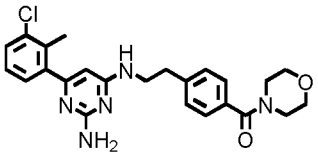
 Example 313	 Example 314	 Example 315
 Example 316	 Example 317	 Example 318
 Example 319	 Example 320	 Example 321
 Example 322	 Example 323	 Example 324
 Example 325	 Example 326	 Example 327
 Example 328	 Example 329	 Example 330
 Example 331	 Example 332	 Example 333
 Example 334	 Example 335	 Example 336

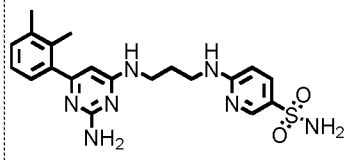
 Example 337	 Example 338	 Example 339
 Example 340	 Example 341	 Example 342
 Example 343	 Example 344	 Example 345
 Example 346	 Example 347	 Example 348
 Example 349	 Example 350	 Example 351
 Example 352	 Example 353	 Example 354
 Example 355	 Example 356	 Example 357
 Example 358	 Example 359	 Example 360

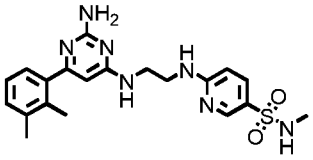
 Example 361	 Example 362	 Example 363
 Example 364	 Example 365	 Example 366
 Example 367	 Example 368	 Example 369
 Example 370	 Example 371	 Example 372
 Example 373	 Example 374	 Example 375
 Example 376	 Example 377	 Example 378
 Example 379	 Example 380	 Example 381
 Example 382	 Example 383	 Example 384

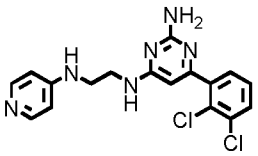
 Example 385	 Example 386	 Example 387
 Example 388	 Example 389	 Example 390
 Example 391	 Example 392	 Example 393
 Example 394	 Example 395	 Example 396
 Example 397	 Example 398	 Example 399
 Example 400	 Example 401	 Example 402
 Example 403	 Example 404	 Example 405
 Example 406	 Example 407	 Example 408

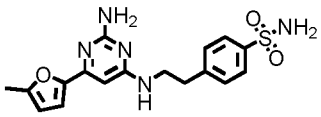
 Example 409	 Example 410	 Example 411
 Example 412	 Example 413	 Example 414
 Example 415	 Example 416	 Example 417
 Example 418	 Example 419	 Example 420
 Example 421	 Example 422	 Example 423
 Example 424	 Example 425	 Example 426
 Example 427	 Example 428	 Example 429
 Example 430	 Example 431	 Example 432

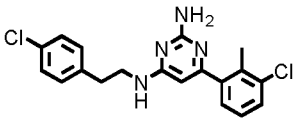
 Example 433	 Example 434	 Example 435
 Example 436	 Example 437	 Example 438
 Example 439	 Example 440	 Example 441
 Example 442	 Example 443	 Example 444
 Example 445	 Example 446	 Example 447
 Example 448	 Example 449	 Example 450
 Example 451	 Example 452	 Example 453
 Example 454	 Example 455	 Example 456

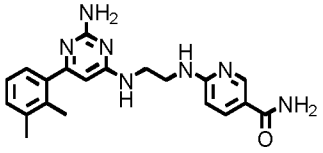

Example 457

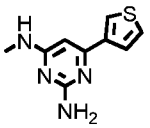

Example 458

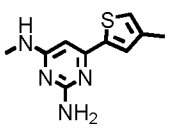

Example 459

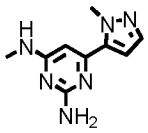

Example 460

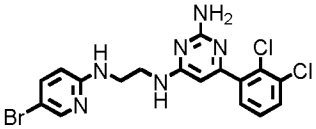

Example 461

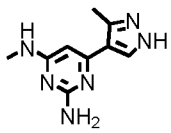

Example 462

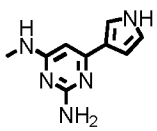

Example 463

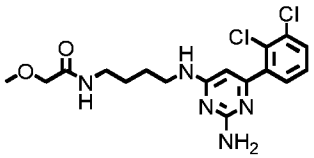

Example 464

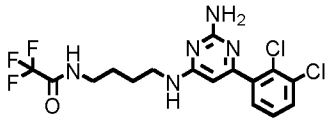

Example 465

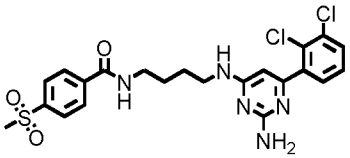

Example 466


Example 467


Example 468


Example 469


Example 470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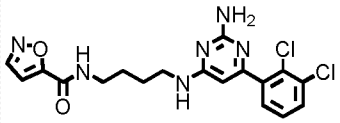
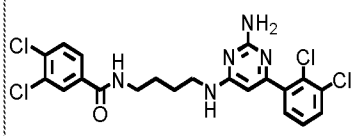

Example 472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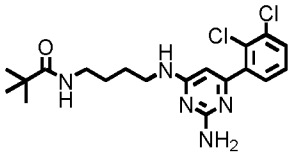
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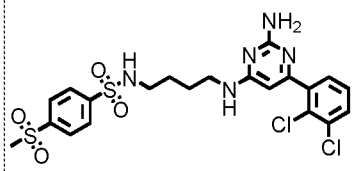
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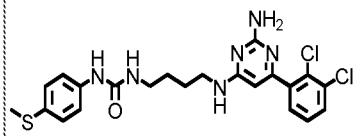
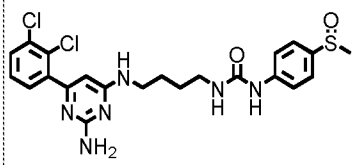
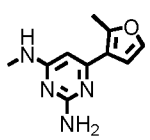
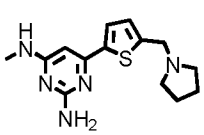
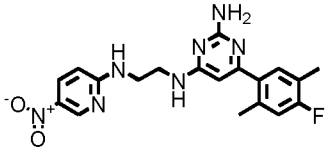
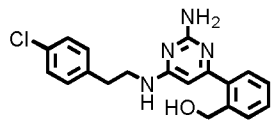
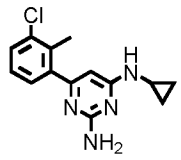
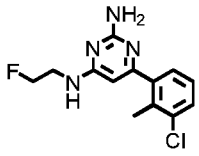
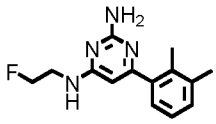
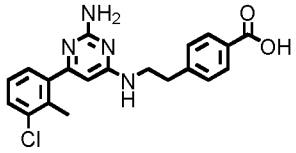
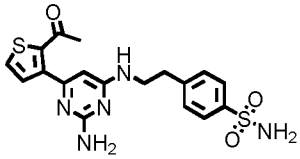
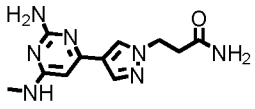
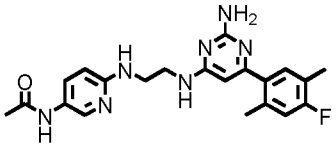
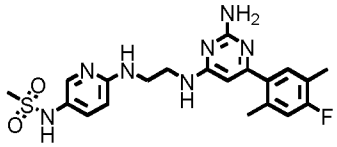
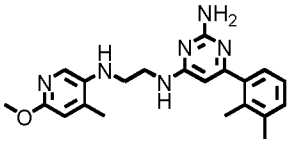
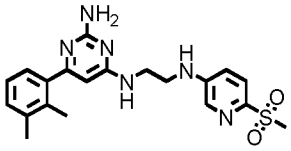
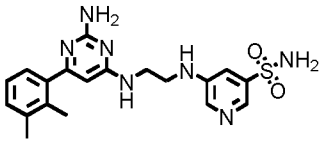
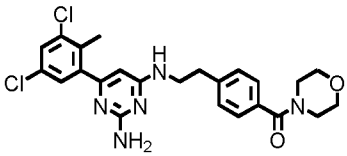
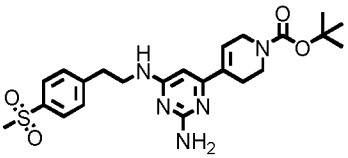
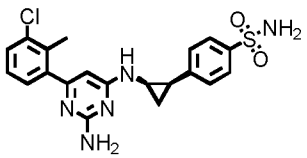
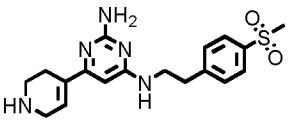
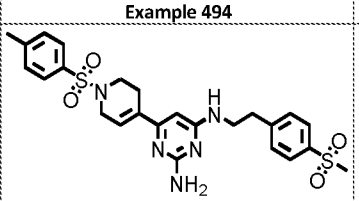
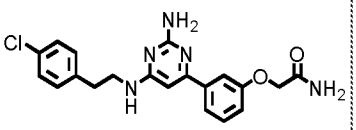
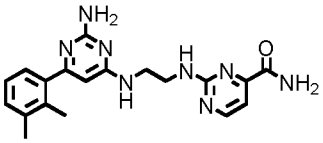
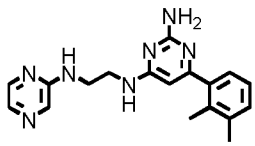
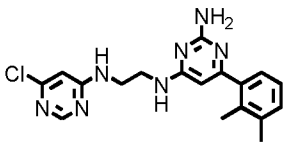
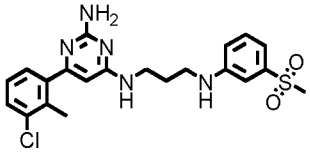
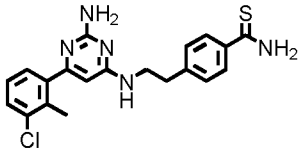
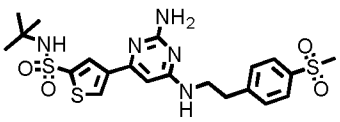

Example 476

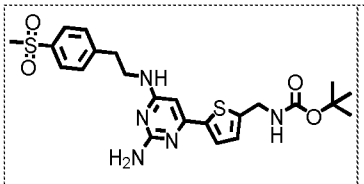
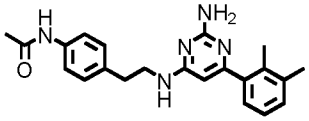
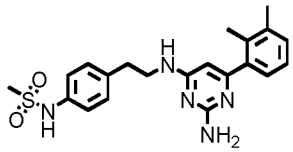
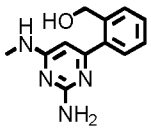
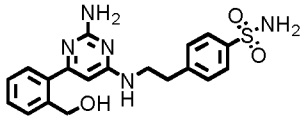
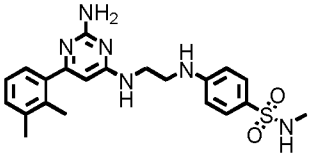
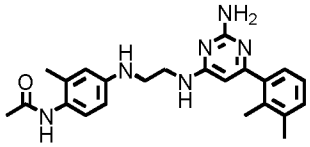
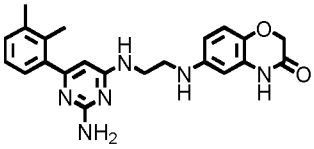
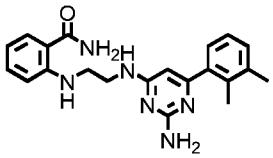
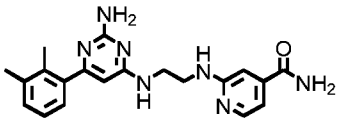
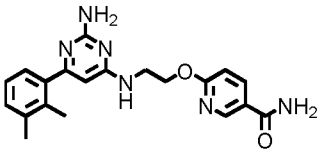
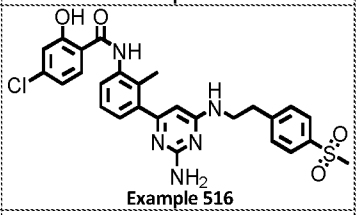
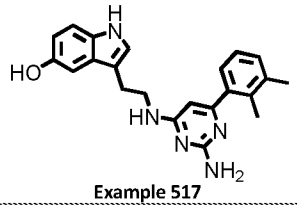
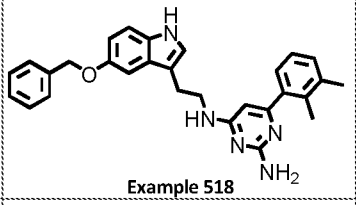
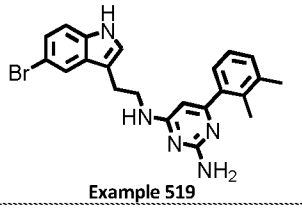
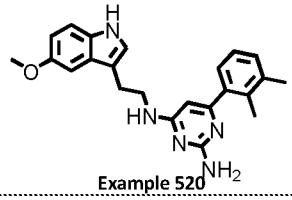
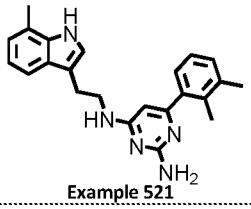
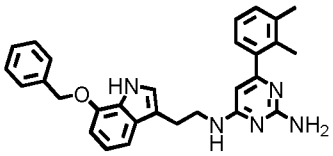
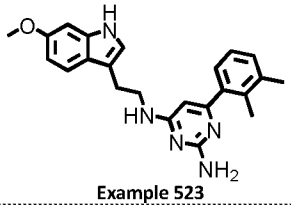
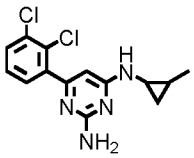
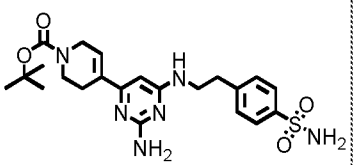
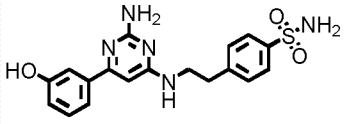
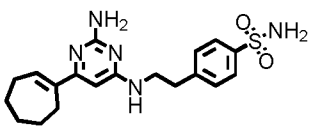
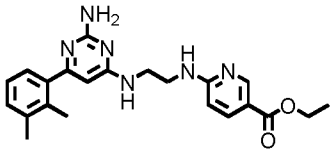

Example 477

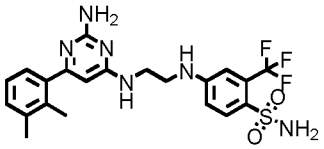
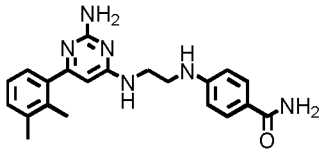
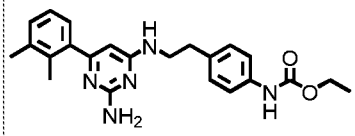
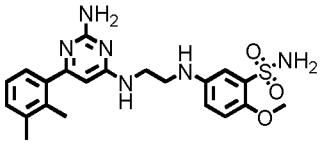
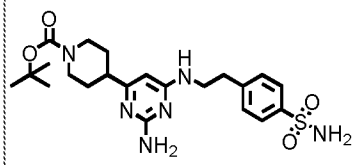
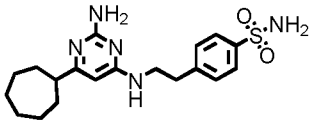
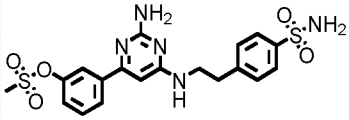
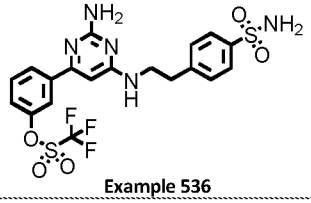
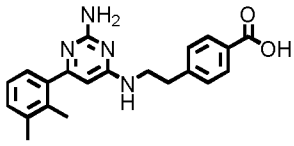
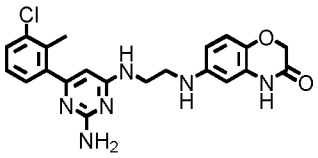
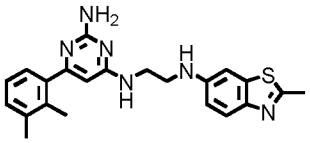
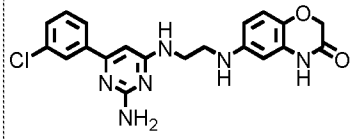
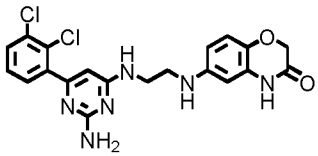
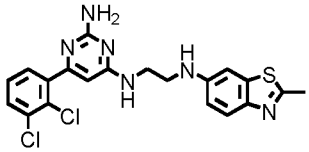
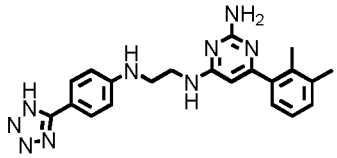
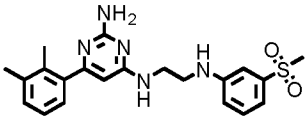
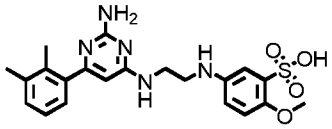
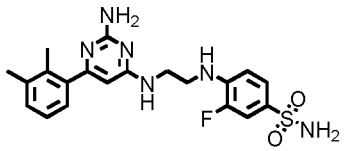
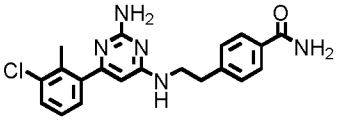
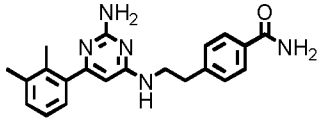
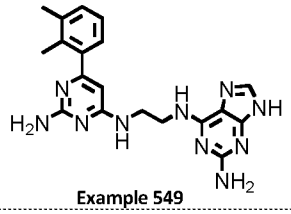
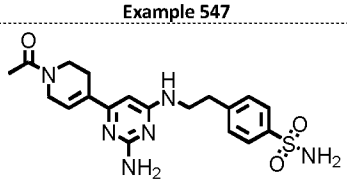
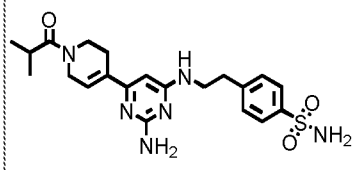
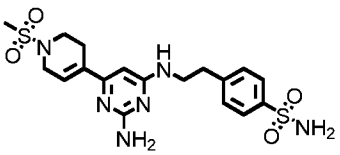

Example 478

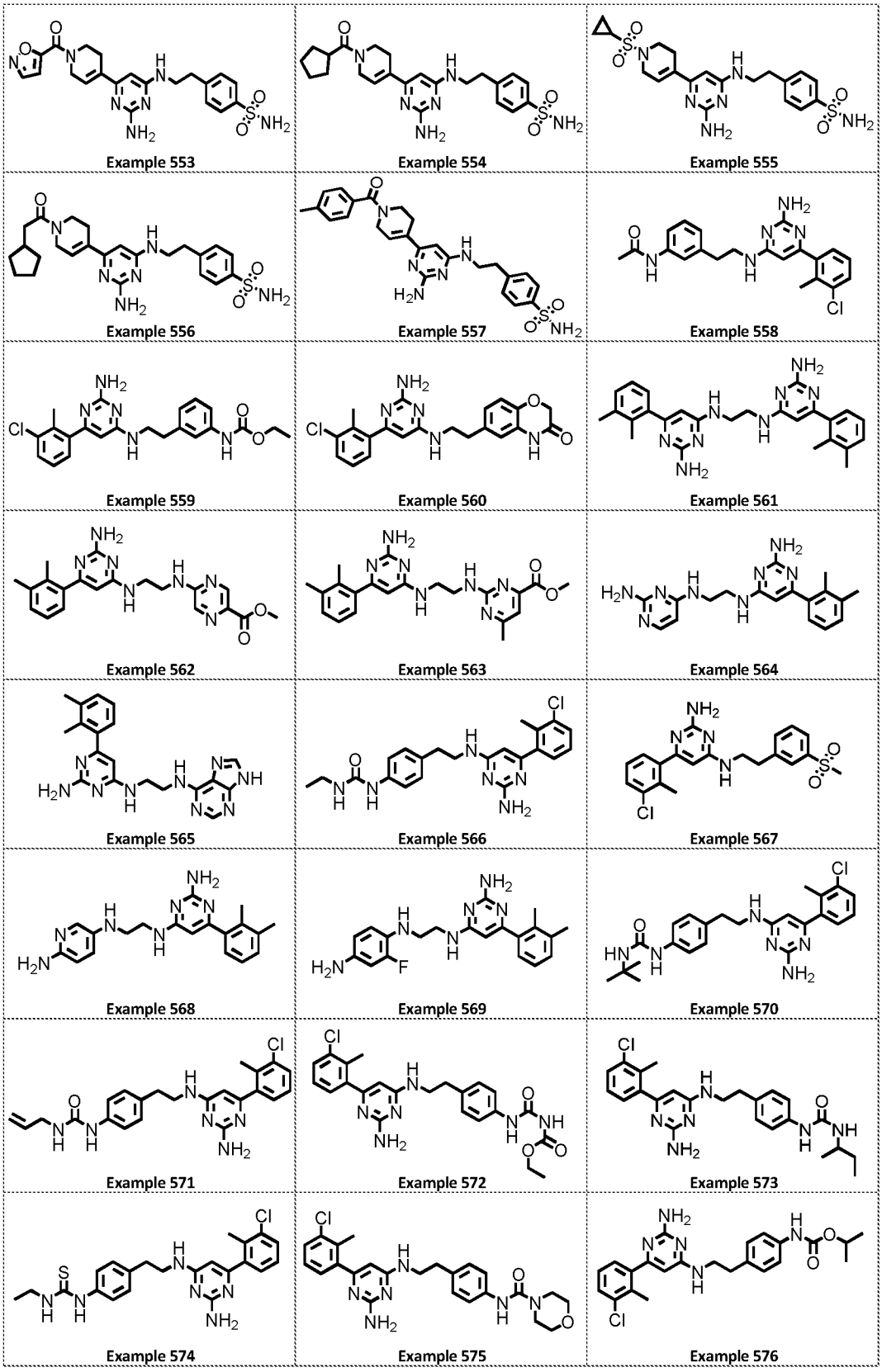

Example 479


Example 480

 Example 481	 Example 482	 Example 483
 Example 484	 Example 485	 Example 486
 Example 487	 Example 488	 Example 489
 Example 490	 Example 491	 Example 492
 Example 493	 Example 494	 Example 495
 Example 496	 Example 497	 Example 498
 Example 499	 Example 500	 Example 501
 Example 502	 Example 503	 Example 504

 Example 505	 Example 506	 Example 507
 Example 508	 Example 509	 Example 510
 Example 511	 Example 512	 Example 513
 Example 514	 Example 515	 Example 516
 Example 517	 Example 518	 Example 519
 Example 520	 Example 521	 Example 522
 Example 523	 Example 524	 Example 525
 Example 526	 Example 527	 Example 528

 Example 529	 Example 530	 Example 531
 Example 532	 Example 533	 Example 534
 Example 535	 Example 536	 Example 537
 Example 538	 Example 539	 Example 540
 Example 541	 Example 542	 Example 543
 Example 544	 Example 545	 Example 546
 Example 547	 Example 548	 Example 549
 Example 550	 Example 551	 Example 552


Example 553
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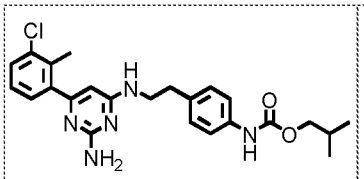
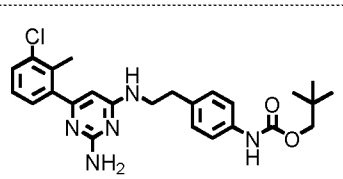
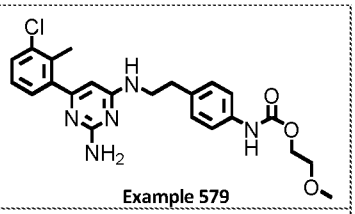
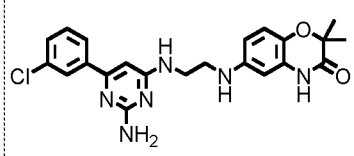
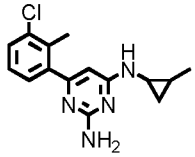
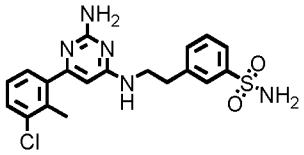

Example 577

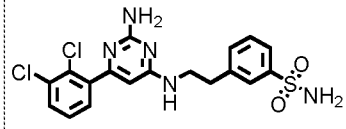

Example 578

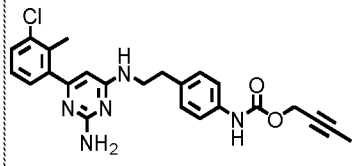

Example 579

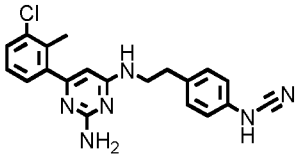

Example 580

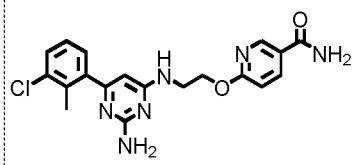

Example 581

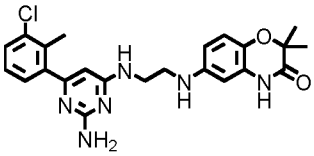

Example 582

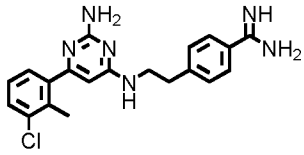

Example 583

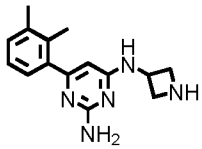

Example 584

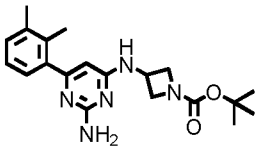

Example 585

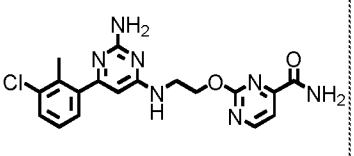

Example 586


Example 587


Example 588


Example 589


Example 590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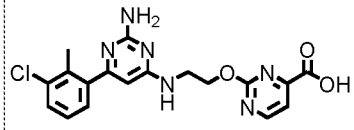
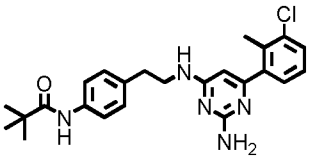
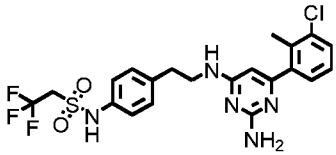
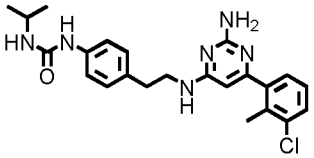
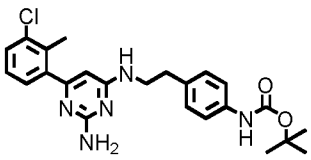
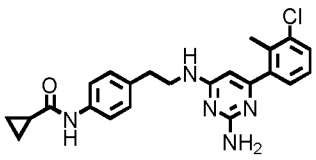

Example 592

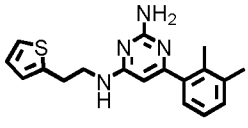

Example 593

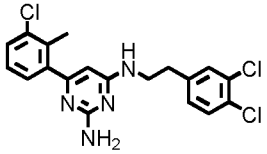

Example 594

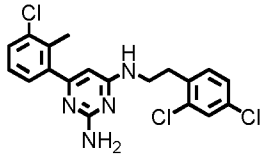

Example 595

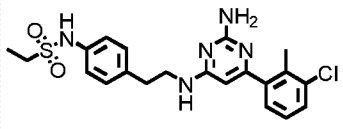
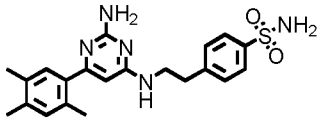
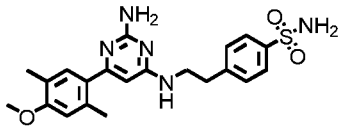
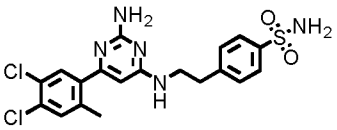
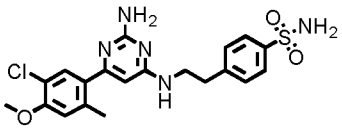
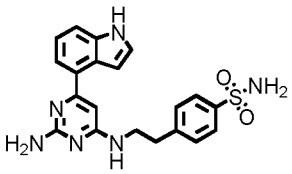
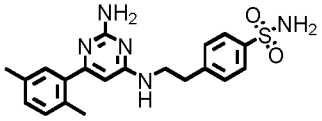
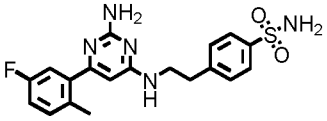
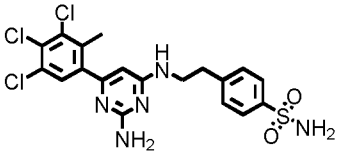
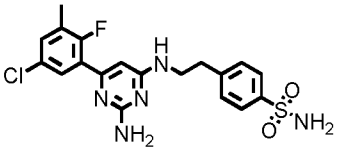
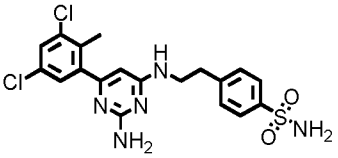
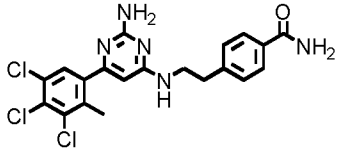
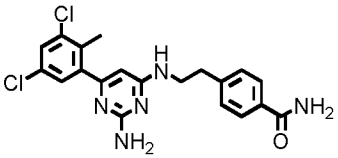
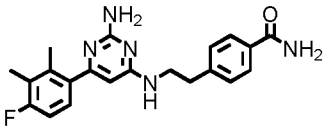
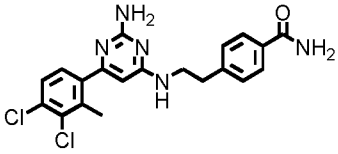
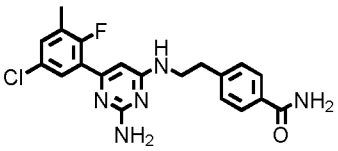
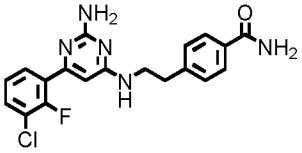
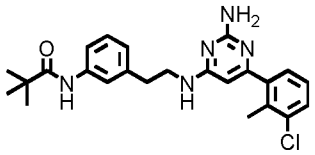
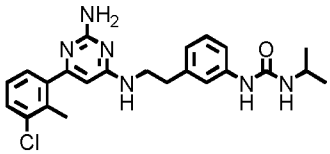
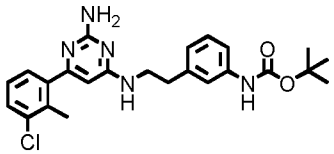
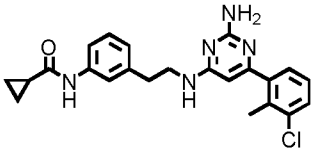
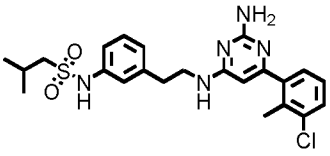
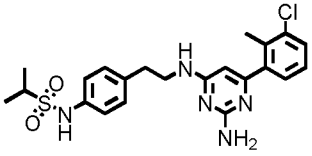
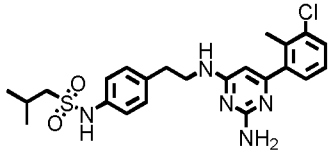

Example 596

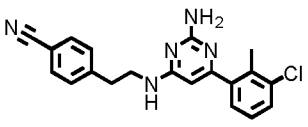
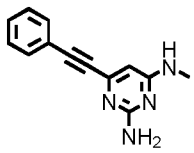
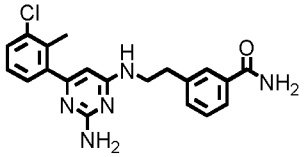
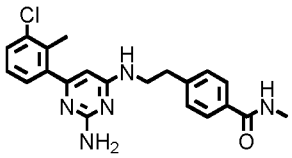
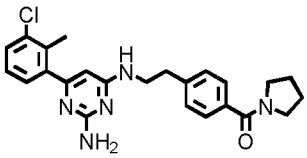
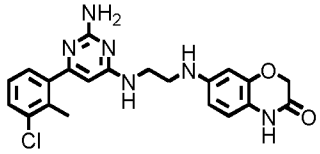
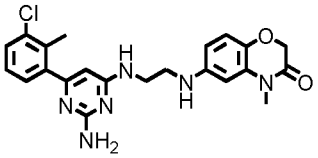
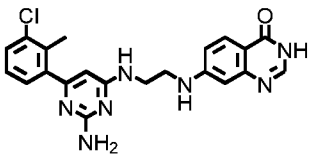
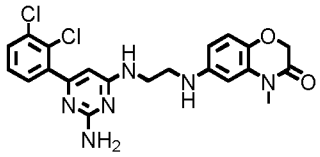
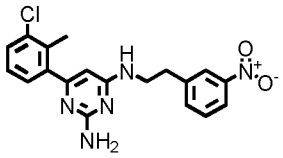
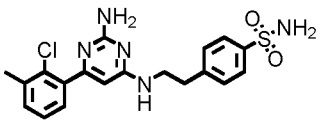
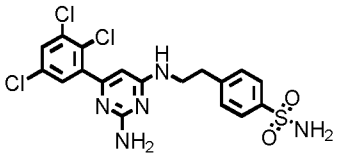
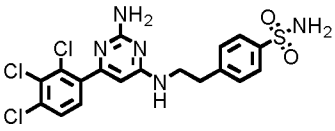
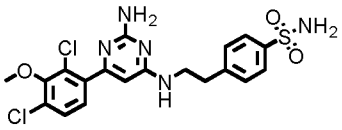
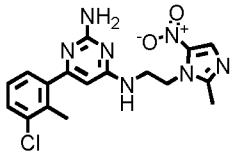
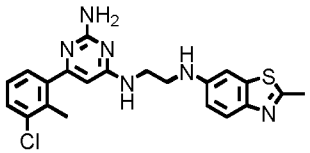
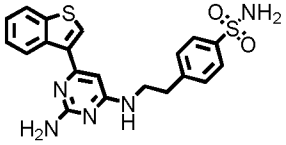
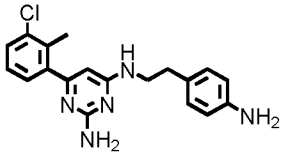
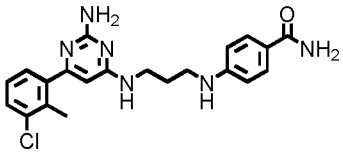
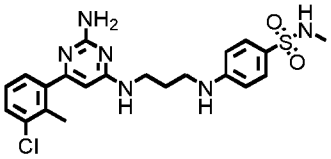
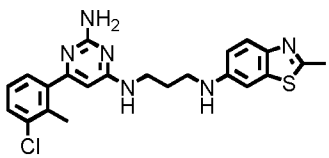
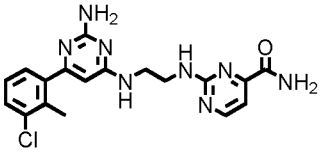
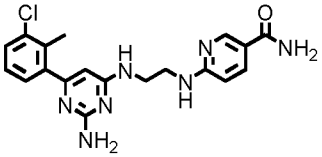
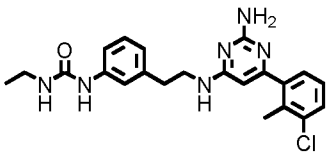

Example 597

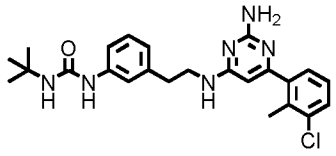
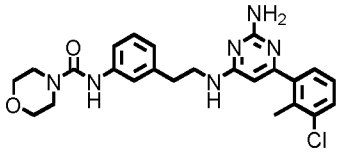
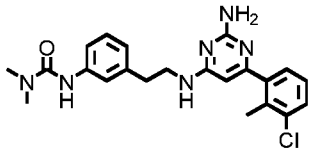
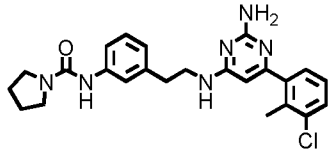
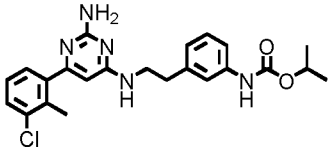
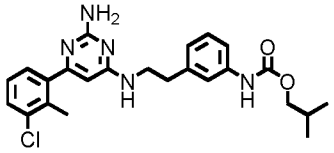
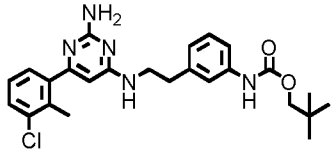
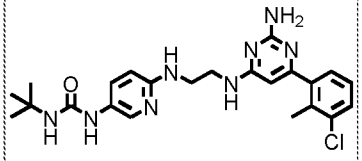
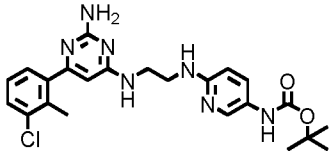
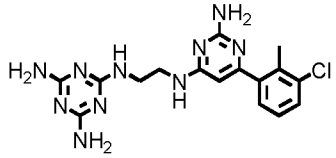
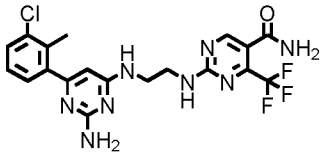
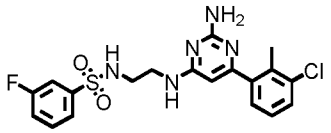
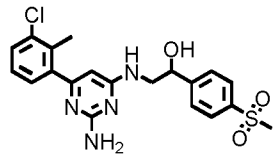
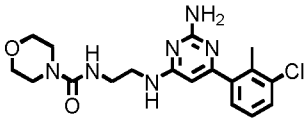
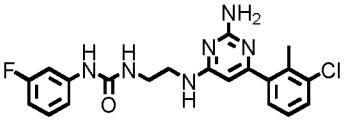
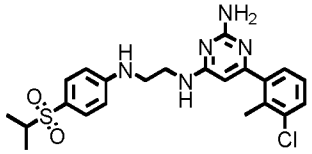
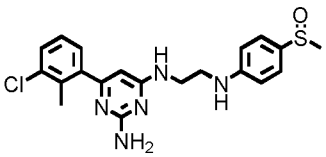
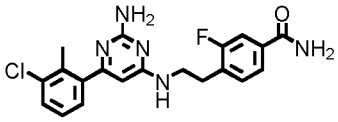
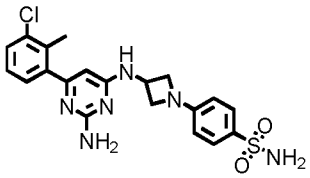
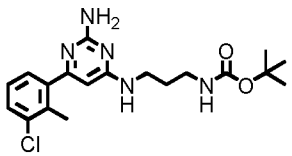
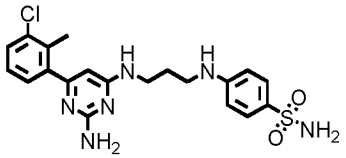
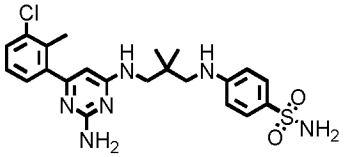
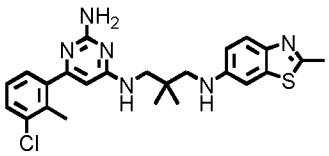
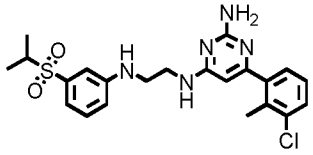

Example 598

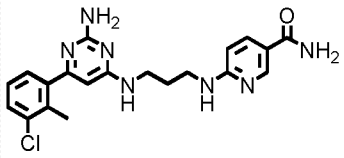
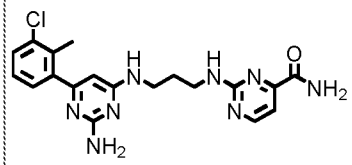
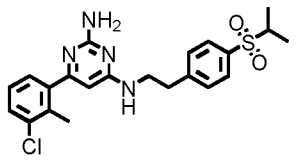
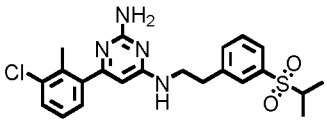
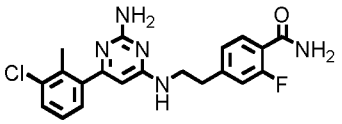
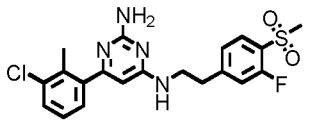
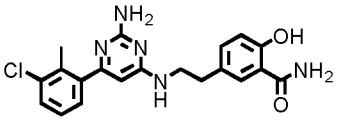
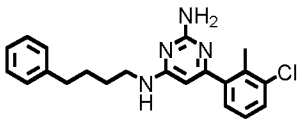
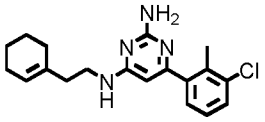
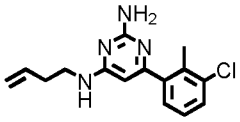
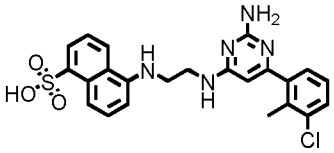
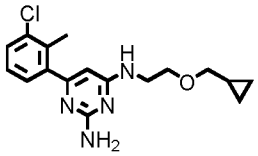
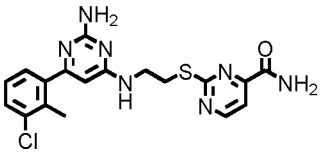
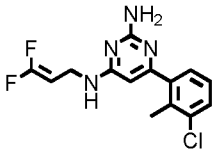
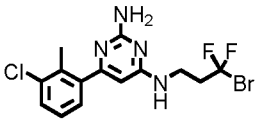
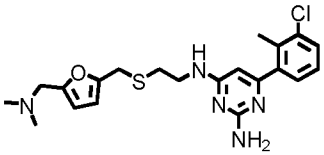
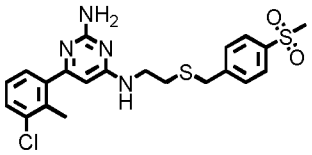
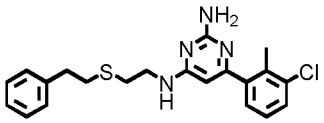
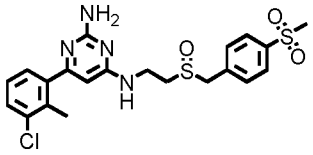
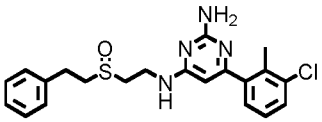
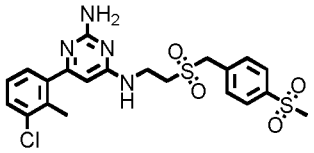
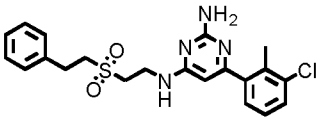
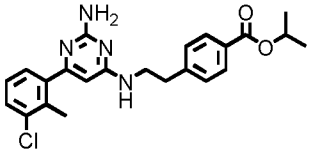
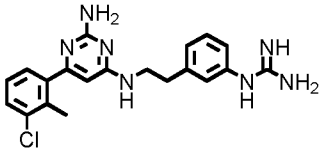

Example 599

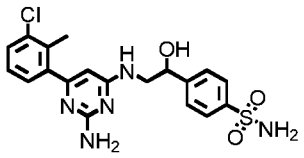

Example 600

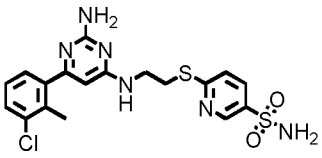
 Example 601	 Example 602	 Example 603
 Example 604	 Example 605	 Example 606
 Example 607	 Example 608	 Example 609
 Example 610	 Example 611	 Example 612
 Example 613	 Example 614	 Example 615
 Example 616	 Example 617	 Example 618
 Example 619	 Example 620	 Example 621
 Example 622	 Example 623	 Example 624

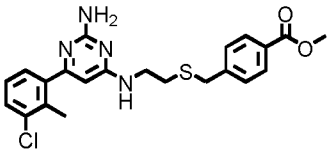
 Example 625	 Example 626	 Example 627
 Example 628	 Example 629	 Example 630
 Example 631	 Example 632	 Example 633
 Example 634	 Example 635	 Example 636
 Example 637	 Example 638	 Example 639
 Example 640	 Example 641	 Example 642
 Example 643	 Example 644	 Example 645
 Example 646	 Example 647	 Example 648

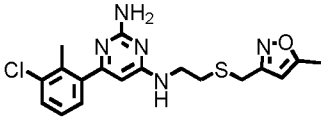
 Example 649	 Example 650	 Example 651
 Example 652	 Example 653	 Example 654
 Example 655	 Example 656	 Example 657
 Example 658	 Example 659	 Example 660
 Example 661	 Example 662	 Example 663
 Example 664	 Example 665	 Example 666
 Example 667	 Example 668	 Example 669
 Example 670	 Example 671	 Example 672

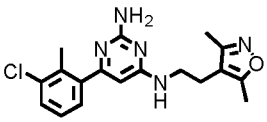
 Example 673	 Example 674	 Example 675
 Example 676	 Example 677	 Example 678
 Example 679	 Example 680	 Example 681
 Example 682	 Example 683	 Example 684
 Example 685	 Example 686	 Example 687
 Example 688	 Example 689	 Example 690
 Example 691	 Example 692	 Example 693
 Example 694	 Example 695	 Example 696

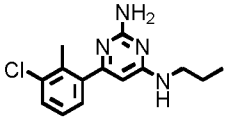

Example 697

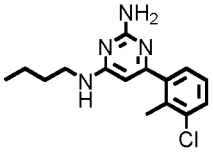

Example 698

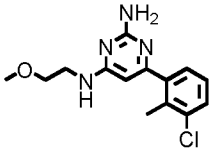

Example 699


Example 700


Example 701


Example 702


Example 703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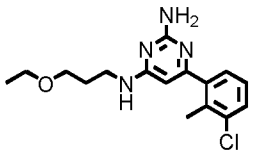
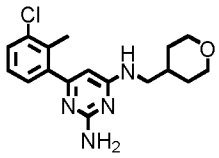
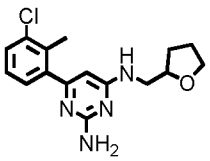
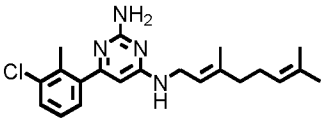
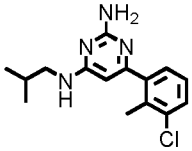
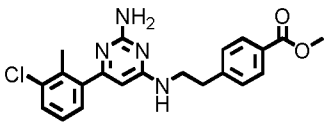

Example 705

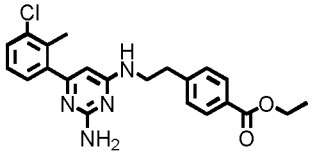

Example 706

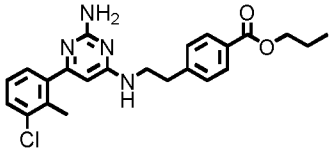

Example 707

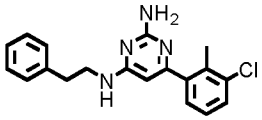

Example 708

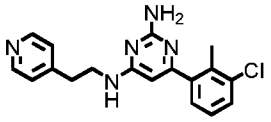

Example 709

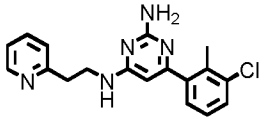

Example 710

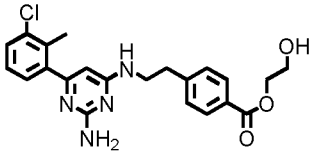

Example 711

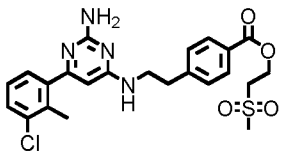

Example 712

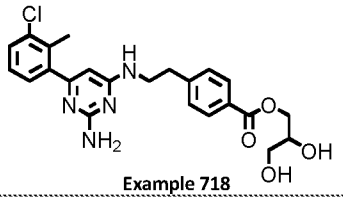

Example 713

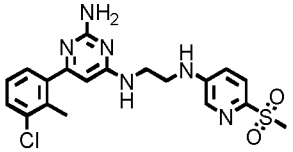

Example 714

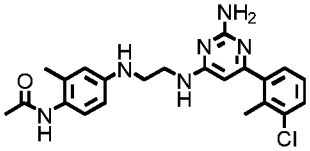

Example 715

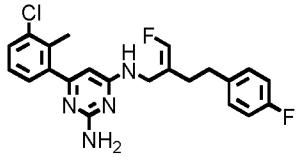
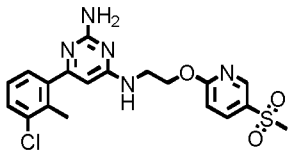
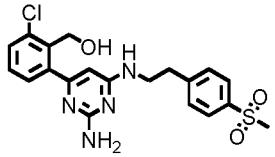
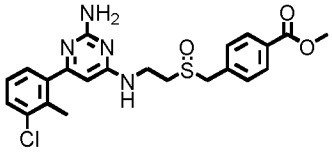
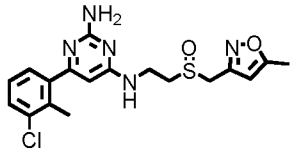
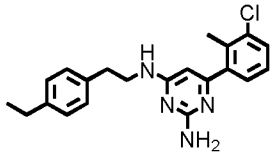
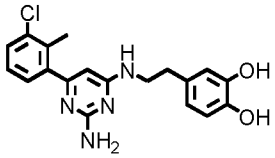
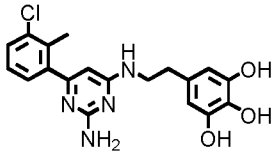
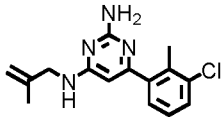
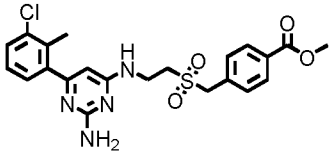
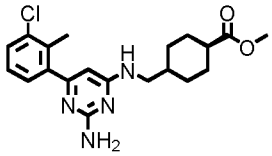
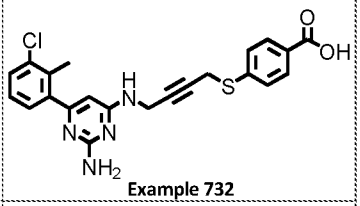
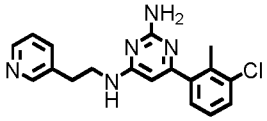
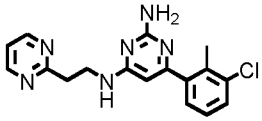
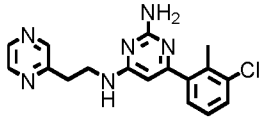
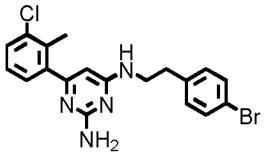
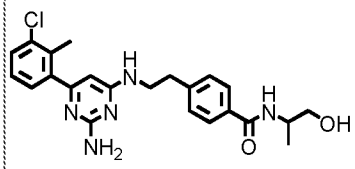
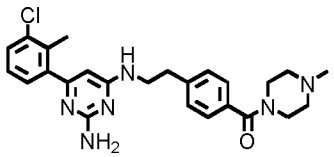
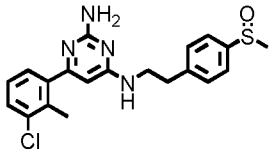
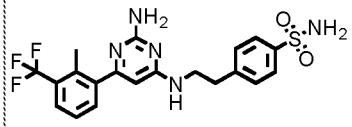
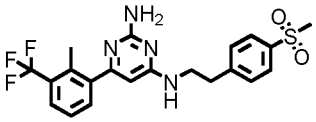
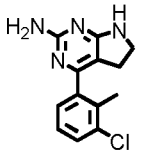
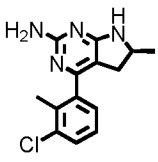
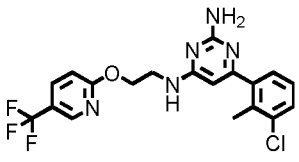

Example 716

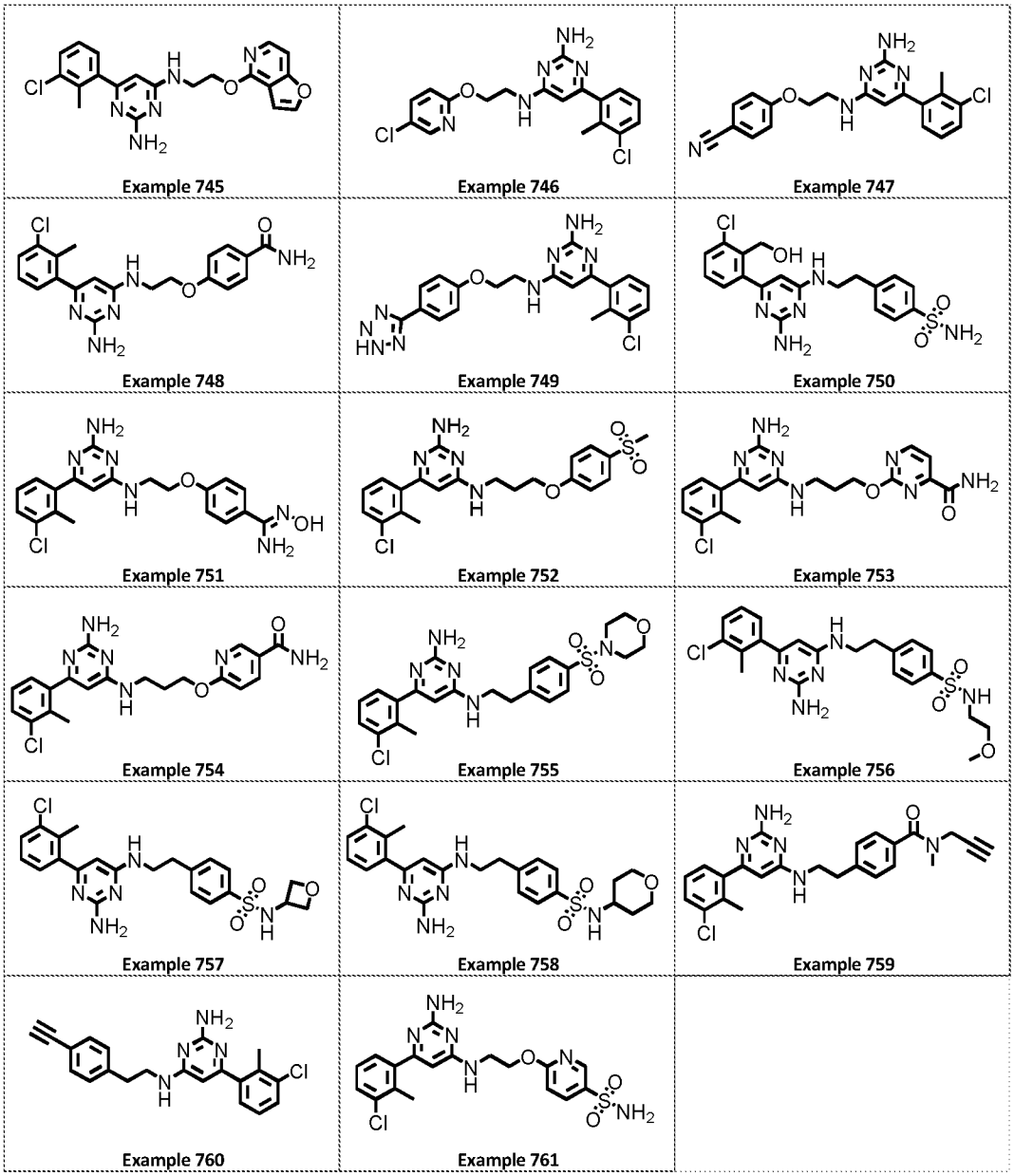

Example 717


Example 718


Example 719


Example 720

 Example 721	 Example 722	 Example 723
 Example 724	 Example 725	 Example 726
 Example 727	 Example 728	 Example 729
 Example 730	 Example 731	 Example 732
 Example 733	 Example 734	 Example 735
 Example 736	 Example 737	 Example 738
 Example 739	 Example 740	 Example 741
 Example 742	 Example 743	 Example 744



Example 745 | Example 746 | Example 747

Example 748 | Example 749 | Example 750

Example 751 | Example 752 | Example 753

Example 754 | Example 755 | Example 756

Example 757 | Example 758 | Example 759

Example 760 | Example 761

Biological Examples

Biological Example 1

MTH1 enzymatic assay and IC50 value determination

MTH1 catalyzes the hydrolysis of dGTP to dGMP and PPi. By coupling the reaction to pyrophosphatase added in excess PPi is converted to Pi that can be detected by using the malachite green assay reagent. Two different formats were used for IC50 determinations in the enzymatic assay, 96- and 384-well format.

96-well method: Briefly, the compound to be analyzed is diluted in DMSO in a 1:3 dilution series generating 12 different compound concentrations giving a final DMSO concentration of 1% in the assay well. MTH1 diluted in assay buffer (100 mM Tris-acetate, 40 mM NaCl, 10 mM magnesium acetate, 1 mM DTT and 0.005% Tween 20) fortified with E.coli pyrophosphatase (0.2 U/ml) is added to a final concentration of 6 nM. dGTP diluted in assay buffer is added to a final concentration of 100 µM. The reaction mixture is incubated for 15 minutes at 22°C. To 100 µl reaction mixture, 25 µl Malachite green assay regent (0.095% Malachite green in 17% H2SO4, 1.5% Ammonium molybdate, 0.17% Tween 20) is added, followed by incubation with shaking for 15 minutes at 22°C. The absorbance of the assay plate is read at 630 nm using a Hidex Sense Multilabel plate reader. The IC50 value is determined by fitting a dose response curve to the data points using nonlinear regression analysis and the equation Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)), where Y is the read absorbance at 630 nm and X is log[compound].

384-well method: The compounds to be tested are nano-dispensed, in 11 concentrations, directly in assay plates, with a final DMSO concentration <1%. The protocol and the reaction mixture are the same as for the 96-well assay, with a total reaction volume of 50 µl/well to which 10 µl of Malachite green reagent is added. All additions to the assay plates are made with multidrop.

Using these approaches the following representative IC50 values were derived. 1, 2, 4, 6, 7, 11, 13, 16, 18, 19, 23, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 43, 44, 46, 47, 48, 49, 50, 51, 52, 53, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 114, 115, 116, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 142, 143, 144, 145, 146, 147, 148, 149, 151, 152, 153, 155, 156, 158, 159, 163, 164, 165, 168, 170, 171, 172, 173, 174, 175, 176, 177, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 226, 227, 228, 230, 231, 232, 233, 234, 235, 239, 240, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 256, 257, 258, 259, 260, 261, 262, 263, 264, 266, 267, 268, 269, 271, 273, 274, 275, 276, 279, 280, 282, 283, 295,

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Examples 3, 8, 9, 10, 17, 22, 24, 25, 42, 45, 54, 60, 95, 96, 102, 113, 117, 119, 150, 154, 157, 160, 162, 169, 178, 199, 212, 225, 229, 236, 238, 241, 242, 255, 265, 270, 272, 278, 284, 285, 286, 287, 288, 290, 291, 292, 293, 294, 298, 302, 306, 318, 319, 320, 339, 340, 347, 353, 354, 358, 360, 365, 366, 368, 369, 373, 377, 378, 380, 383, 384, 387, 390, 392, 395, 410, 413, 423, 446, 459, 467, 496, 504, 533, 535, 590, 592, 662, 691, 693, 694, 724, 730 and 734 had IC_{50}'s of between 200 nM and 2 μM.

Examples 5, 12, 14, 15, 20, 21, 112, 161, 166, 167, 179, 180, 181, 182, 237, 277, 281, 289, 299, 345, 372, 396, 399, 589, 667, 692 and 725 had IC_{50}'s of between 2 µM and 10 µM.

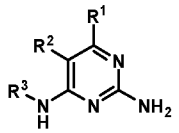
Biological Example 2

Cellular assay and IC50 value determination

Primary T-lymphocytes are isolated from donated human blood and thereafter activated with CD3/CD28 Dynabeads. The T-lymphocytes are treated with an MTH1 inhibitor, positive control or vehicle for 24-96 hrs. Cell viability can be measured by using standard assays, such as for instance a resazurin assay. In some experiments, the cells are stained with Cell Trace Violet at the start of the culture. The dye is diluted as the cells divide and gives a measurement of cell proliferation (see Fig.1 for an example).

Claims

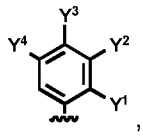
1. A compound of formula I,



(I)

or a pharmaceutically acceptable salt thereof,
for use in the treatment of autoimmune diseases and inflammatory conditions,
wherein:

R^1 represents

(i)  , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine ring of the compound of formula I via a carbon atom of the heteroaryl, which heteroaryl is optionally substituted by one or more groups selected from Y^5, or

(iv) -ethynyl-Y^6;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2; or

R^1 represents

(v) a 3- to 8-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7;

R^2 represents hydrogen, halogen, -CN or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J; or

R^1 is as defined herein above; and

R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more groups selected from Z^3 and optionally substituted by -X-L-J;

X represents -C_{1-6}alkylene-, optionally substituted by one or more T^1, or -$(C(R^A)_2)_p$-C_{2-5}heterocycloalkylene-$(C(R^A)_2)_q$-, where the heterocycloalkylene is optionally substituted by one or more T^2;

L represents a single bond or -L^1-L^2-;

L^1 represents -$N(R^B)$-, -O-, -$S(O)_m$-, -$C(O)N(R^C)$-, -$N(R^D)C(O)$-, -$S(O)_nN(R^E)$-, -$N(R^F)S(O)_n$- or -$N(R^G)C(O)N(R^H)$-;

L^2 represents a single bond or -C_{1-6}alkylene-;

J represents

(i) a 6- to 10-membered aryl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X, or

(ii) a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which heteroaryl contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which heteroaryl is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y;

Y^1 represents hydrogen, halogen, -CN, R^a, -A-$C(Q)R^b$, -A-$C(Q)N(R^c)R^d$, -A-$C(Q)OR^e$, -A-$S(O)_nR^f$, -A-$S(NR^g)(O)R^h$, -A-$S(O)_nN(R^i)R^j$, -A-$S(O)_nOR^k$, -$B(OR^l)_2$, -N_3, -NO_2, -OR^m -SR^n;

Y^2, Y^3 and Y^4 each independently represents hydrogen, halogen, R^a, -A-$C(Q)R^b$, -A-$C(Q)N(R^c)R^d$, -A-$C(Q)OR^e$, -A-$S(O)_nR^f$, -A-$S(NR^g)(O)R^h$, -A-$S(O)_nN(R^i)R^j$, -A-$S(O)_nOR^k$, -$B(OR^l)_2$, -N_3, -NO_2, -OH, -OR^m or -SR^n;

Y^5 represents halogen, R^a, -A-$C(Q)R^b$, -A-$C(Q)N(R^c)R^d$, -A-$C(Q)OR^e$, -A-$S(O)_nR^f$, -A-$S(NR^g)(O)R^h$, -A-$S(O)_nN(R^i)R^j$, -A-$S(O)_nOR^k$, -$B(OR^l)_2$, -N_3, -NO_2, -OH, -OR^m or -SR^n;

Y^6 represents aryl or heteroaryl, both optionally substituted by one or more groups selected from halogen, -CN, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(N$R^g$)(O)$R^h$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -B(O$R^l$)$_2$, -$N_3$, -$NO_2$, -OH, -O$R^m$ and -SR^n;

Y^7 represents halogen, R^a, -A-C(Q)R^b, -A-C(Q)N(R^c)R^d, -A-C(Q)OR^e, -A-S(O)$_n$$R^f$, -A-S(O)$_n$N($R^i$)$R^j$, -A-S(O)$_nOR^k$, -OH, -O$R^m$, or Q;

Q represents =O, =S, =NR^o, =NN(R^p)R^q, =N(OR^r), =NS(O)$_2$N(R^s)R^t or =C(H)NO_2;

A represents a single bond, -N(R^l)-, -C(Q)N(R^J)- or -O-;

each R^a, R^f, R^h and R^m independently represents C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3;

each R^b, R^c, R^d, R^e, R^g, R^i, R^j, R^k, R^l, R^o, R^p, R^q, R^r, R^s and R^t independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more groups selected from W^1, heterocycloalkyl optionally substituted by one or more groups selected from W^2 or aryl or heteroaryl both optionally substituted by one or more groups selected from W^3; or

any two R^c and R^d, R^i and R^j, R^p and R^q and/or R^s and R^t are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more groups selected from W^2, C_{1-3}alkyl optionally substituted by one or more groups selected from W^1, and =O; or

two R^l are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is

substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

W^1 represents halogen, -CN, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$,$-OR^{j1}$ or =O;

W^2 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-N(R^{h1})R^{i1}$, $-OR^{j1}$ or =O;

W^3 represents halogen, -CN, R^{a1}, $-A^1-C(O)R^{b1}$, $-A^1-C(O)N(R^{c1})R^{d1}$, $-A^1-C(O)OR^{e1}$, $-A^1-S(O)_nR^{f1}$, $-A^1-S(O)_nOR^{g1}$, $-OR^{j1}$, $-A^1-S(NR^{k1})(O)R^{l1}$, $-A^1-S(O)_nN(R^{m1})R^{n1}$, $-N_3$, $-NO_2$, $-SR^{o1}$ or =O;

A^1 represents a single bond, $-N(R^K)-$ or -O-;

each R^{a1}, R^{f1} and R^{l1} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{g1}, R^{h1}, R^{i1}, R^{j1}, R^{k1}, R^{m1}, R^{n1} and R^{o1} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro; or

any two R^{c1} and R^{d1}, R^{h1} and R^{i1} and/or R^{m1} and R^{n1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

Z^1 represents halogen, -CN, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$, $-SR^{o2}$ or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

Z^2 represents halogen, -CN, R^{a2}, $-A^2-C(Q^1)R^{b2}$, $-A^2-C(Q^1)N(R^{c2})R^{d2}$, $-A^2-C(Q^1)OR^{e2}$, $-A^2-S(O)_nR^{f2}$, $-A^2-S(O)_nOR^{g2}$, $-A^2-S(NR^{h2})(O)R^{i2}$, $-A^2-S(O)_nN(R^{j2})R^{k2}$, $-N(R^{l2})R^{m2}$, $-OR^{n2}$ or $=Q^1$;

Z^3 represents R^{a2} or $=Q^1$;

Q^1 represents =O, =S, $=NR^{p2}$, $=NN(R^{q2})R^{r2}$, $=N(OR^{s2})$, $=NS(O)_2N(R^{t2})R^{u2}$ or $=C(H)NO_2$;

A^2 represents a single bond, $-N(R^L)-$, $-C(Q^1)N(R^M)-$ or -O-;

each R^{a2}, R^{f2}, R^{i2}, R^{n2} and R^{o2} independently represents C_{1-6}alkyl optionally substituted by one or more groups selected from W^4 or heterocycloalkyl optionally substituted by one or more groups selected from W^5;

R^{m2} represents C_{2-6}alkyl optionally substituted by one or more groups selected from W^4;

each R^{b2}, R^{c2}, R^{d2}, R^{e2}, R^{g2}, R^{h2}, R^{j2}, R^{k2}, R^{l2}, R^{p2}, R^{q2}, R^{r2}, R^{s2}, R^{t2} and R^{u2} independently represents hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from W^4, heterocycloalkyl optionally substituted by one or more groups selected from W^5; or

any two R^{c2} and R^{d2}, R^{j2} and R^{k2}, R^{l2} and R^{m2}, R^{q2} and R^{r2} and/or R^{t2} and R^{u2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more groups selected from W^5, C_{1-3}alkyl optionally substituted by one or more groups selected from W^4, and =O;

W^4 represents halogen, -CN, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^5 represents halogen, -CN, R^{a3}, $-A^3-C(O)R^{b3}$, $-A^3-C(O)N(R^{c3})R^{d3}$, $-A^3-C(O)OR^{e3}$, $-A^3-S(O)_nR^{f3}$, $-A^3-S(O)_nOR^{g3}$, $-OR^{h3}$, =O or W^6;

W^6 represents phenyl or heteroaryl, both optionally substituted by one or more groups selected from halogen and R^{a3};

A^3 represents a single bond, -N(R^L)- or -O-;

each R^{a3} and R^{f3} independently represents C_{1-6} alkyl optionally substituted by one or more fluoro;

each R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{g3} and R^{h3} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more fluoro; or

R^{c3} and R^{d3} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatoms and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O;

D^1 and D^2 represent R^{a4}, -A^4-C(Q^2)R^{b4}, -A^4-C(Q^2)N(R^{c4})R^{d4}, -A^4-C(Q^2)OR^{e4}, -A^4-S(O)$_n$$R^{f4}$, -$A^4$-S(O)$_n$C(O)$R^{g4}$, -$A^4$-S(N$R^{h4}$)(O)$R^{i4}$, -$A^4$-S(O)$_n$N($R^{j4}$)$R^{k4}$, -$A^4$-S(O)$_nOR^{l4}$, -B(O$R^{m4}$)$_2$, -$N_3$, -N($R^{n4}$)$R^{o4}$, -N(H)CN, -$NO_2$, -$ONO_2$, -O$R^{p4}$, -S$R^{q4}$ or, when J is partly aromatic, =Q^2;

Q^2 represents =O, =S, =NR^{r4}, =NN(R^{s4})R^{t4}, =N(OR^{u4}), =NS(O)$_2$N(R^{v4})R^{w4} or =C(H)NO_2;

A^4 represents a single bond, -N(R^M)-, -C(Q)N(R^N)- or -O-;

each R^X and R^Y independently represent halogen, -CN, R^{a4}, -N(R^{n4})R^{o4}, -NO_2, -OR^{p4} or =O;

R^{c4} represents hydrogen, R^{a4}, -C(O)OR^{e4}, -S(O)$_n$$R^{f4}$, -S(O)$_n$N($R^{j4}$)$R^{k4}$, -N($R^{n4}$)$R^{o4}$ or -OR^{p4};

each R^{a4}, R^{f4} and R^{i4} independently represent C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more

groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4;

each R^{b4}, R^{d4}, R^{e4}, R^{g4}, R^{h4}, R^{j4}, R^{k4}, R^{l4}, R^{m4}, R^{n4}, R^{o4}, R^{p4}, R^{q4}, R^{r4}, R^{s4}, R^{t4}, R^{u4}, R^{v4} and R^{w4} independently represent hydrogen, C_{1-6}alkyl optionally substituted by one or more groups selected from G^1, heterocycloalkyl optionally substituted by one or more groups selected from G^2, aryl optionally substituted by one or more groups selected from G^3 or heteroaryl optionally substituted by one or more groups selected from G^4; or

any two R^{c4} and R^{d4}, R^{j4} and R^{k4}, R^{n4} and R^{o4}, R^{s4} and R^{t4} and/or R^{v4} and R^{w4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one heteroatom and which ring optionally is substituted by one or more groups selected from fluoro, C_{1-3}alkyl optionally substituted by one or more fluoro, and =O; or

two R^{m4} are linked together to form, along with the boron, and the oxygen atoms to which they are attached, a 5- to 8-membered heterocyclic ring, which ring optionally contains one or more further heteroatoms and which ring optionally is substituted by one or more groups independently selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each G^1 is independently selected from halogen, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^2 is independently selected from halogen, R^{a5}, -CN, $-N(R^{b5})R^{c5}$, $-N(H)C(O)R^{d5}$, $-N(H)S(O)_nR^{h5}$, $-OR^{k5}$, $-S(O)_mR^{l2}$ or =O;

each G^3 and G^4 are independently selected from halogen, -CN, R^{a5}, $-N(R^{b5})R^{c5}$, $-A^5-C(O)R^{d5}$, $-A^5-C(O)N(R^{e5})R^{f5}$, $-A^5-C(O)OR^{g5}$, $-A^5-S(O)_nR^{h5}$, $-A^5-S(O)_nN(R^{i5})R^{j5}$, $-OR^{k5}$ or =O;

A^5 represents a single bond or -N(H)-;

R^{a5} represents C_{1-6} alkyl optionally substituted by one or more halogens;

each R^{b5}, R^{c5}, R^{d5}, R^{e5}, R^{f5}, R^{g5}, R^{h5}, R^{i5}, R^{j5}, R^{k5} and R^{l5} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more halogens; or

any two R^{b5} and R^{c5}, R^{e5} and R^{f5} and/or R^{i5} and R^{j5} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains one further heteroatom and which ring optionally is substituted by one or more groups selected from halogen, C_{1-3}alkyl optionally substituted by one or more halogens, and =O;

each R^{A}, R^{B}, R^{C}, R^{D}, R^{E}, R^{F}, R^{G}, R^{H}, R^{I}, R^{J}, R^{K}, R^{L}, R^{M} and R^{N} independently represents hydrogen or C_{1-3} alkyl optionally substituted by one or more fluoro;

T^1 represents halogen, -CN, $-N(R^{b6})R^{c6}$ or $-OR^{d6}$;

T^2 represents halogen, -CN, R^{a6}, $-OR^{d6}$ or =O;

each R^{a6} independently represents C_{1-6}alkyl optionally substituted by one or more halogens;

each R^{b6}, R^{c6} and R^{d6} independently represents hydrogen or C_{1-6}alkyl optionally substituted by one or more halogens; or

R^{b6} and R^{c6} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring;

each p and q independently represents 0, 1 or 2, provided that the sum of p and q is 0, 1 or 2;

each m independently represents 0, 1 or 2;

each n independently represents 1 or 2;

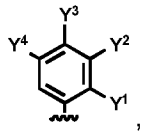
provided that when X represents $-CH_2CH_2-$, L represents $-L^1-L^2-$, L^1 represents -N(H)- or -N(Me)-, L^2 represents a single bond and J represents 4-pyrimidinyl,

and said 4-pyrimidinyl is unsubstituted or substituted with $-CH_3$, $-NH_2$ or $-N(H)CH_2CH(CH_3)_2$, then R^1 does not represent phenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 5-chloro-2-methoxyphenyl, and

provided that formula I does not represent (*S*)-*N*^{4}-(1-(2,4-difluorophenyl)ethyl)-6-(pyrazolo[1,5-*a*]pyrimidin-3-yl)pyrimidine-2,4-diamine.

2. A compound for use as claimed in Claim 1 wherein

R^1 represents

(i)  , or

(ii) a 6-membered heteroaryl substituted by one or more groups selected from Y^5, or

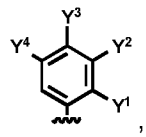
(iii) a 5- to 10-membered monocyclic or bicyclic heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is optionally substituted by one or more groups selected from Y^5;

R^2 represents hydrogen or C_{1-3}alkyl optionally substituted by one or more fluoro; and

R^3 represents -X-L-J, $-C_{1-12}$alkyl optionally substituted by one or more groups selected from Z^1 or heterocycloalkyl optionally substituted by one or more groups selected from Z^2.

3. A compound for use as claimed in Claim 2 wherein

R^1 represents

 ,

at least one of Y^1, Y^2, Y^3 and Y^4 is other than hydrogen;

R^2 represents hydrogen or methyl;

R^3 represents -X-L-J or $-C_{1-6}$alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2;

Y^1 represents hydrogen, halogen, -CN, R^a or $-OR^m$; and

Y^2, Y^3 and Y^4 each independently represent hydrogen, halogen, R^a, -A-C(Q)R^b, -C(Q)N(R^c)R^d, -C(Q)OR^e, -A-S(O)$_n$$R^f$, -S(O)$_n$N($R^i$)$R^j$, -OH or -O$R^m$.

4. A compound for use as claimed in Claim 3 wherein at least two of Y^1, Y^2, Y^3 and Y^4 are other than hydrogen.

5. A compound for use as claimed in Claim 4 wherein
Y^3 and Y^4 are hydrogen; and
Y^1 and Y^2 are independently selected from fluoro, chloro, -Me or -CF_3.

6. A compound for use as claimed in Claim 2 wherein
R^1 represents a 6-membered heteroaryl substituted by one or more groups selected from Y^5;
R^2 represents hydrogen; and
R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

7. A compound for use as claimed in Claim 2 wherein
R^1 represents a 5-membered monocyclic heteroaryl, connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, and optionally substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by Z^1.

8. A compound for use as claimed in Claim 2 wherein
R^1 represents a bicyclic heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which ring is optionally substituted by one or more Y^5;
R^2 represents hydrogen; and
R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

9. A compound for use as claimed in Claim 1 wherein
R^1 represents -ethynyl-Y^6;
R^2 represents hydrogen; and

R^3 represents -X-L-J or -C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

10. A compound for use as claimed in any one of Claims 1 to 11 wherein R^3 represents -X-L-J.

11. A compound for use as claimed in Claim 1 wherein
R^1 represents a 3- to 8-membered nonaromatic ring, which ring optionally contains one or two heteroatoms and/or one or two double bonds, and which ring is optionally substituted by one or more groups selected from Y^7;
R^2 represents hydrogen or C_{1-3}alkyl optionally substituted by one or more fluoro; and
R^3 represents -X-L-J.

12. A compound for use as claimed in Claim 1 wherein
R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more groups selected from Z^3 and optionally substituted by -X-L-J.

13. A compound for use as claimed in any of Claims 10 to 12 wherein
X represents -CH_2-, -CH_2CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH(Me)-, -CH(Me)CH_2-, -$CH_2CH_2CH_2$-, -CH(Me)CH_2CH_2-, -$CH_2CH_2CH_2CH_2$-, -$CH_2C(CH_3)_2CH_2$-, -cyclopropylene- or .

14. A compound for use as claimed in Claim 13
wherein X represents -CH_2CH_2-, -$CH_2CH_2CH_2$- or -cyclopropylene-.

15. A compound for use as claimed in any one of Claims 1 to 14 wherein L represents -L^1-L^2-.

16. A compound for use as claimed in Claim 15 wherein
L^1 represents -N(H)-, -O-, -SO_2-, -C(O)N(H)-, -SO_2N(H)- or -N(H)C(O)N(H)-.

17. A compound for use as claimed in Claim 16 wherein

L^1 represents -N(H)-, -O- or -N(H)C(O)N(H)-.

18. A compound for use as claimed in any one of Claims 1 to 17 wherein L^2 represents a single bond or -C_{1-6}alkylene-.

19. A compound for use as claimed in Claim 18 wherein L^2 represents a single bond.

20. A compound for use as claimed in Claim 18 wherein L^2 represents -CH_2- or -CH_2CH_2-.

21. A compound for use as claimed in any one of Claims 1 to 14 wherein L represents a single bond.

22. A compound for use as claimed in any one of Claims 1 to 21 wherein J represents phenyl optionally substituted by D^1 and optionally substituted by one or more groups selected from R^X.

23. A compound for use as claimed in any one of Claims 1 to 21 wherein J represents a 5- to 11-membered monocyclic or bicyclic heteroaryl ring, which ring contains 1 to 3 nitrogen atoms, and/or one oxygen atom and/or one or two sulfur atoms and which ring is optionally substituted by D^2 and optionally substituted by one or more groups selected from R^Y.

24. A compound for use as claimed in any one of Claims 1, 2 and 5 to 11 wherein R^3 represents -C_{1-6}alkyl optionally substituted by one or more groups selected from Z^1.

25. A compound for use as claimed in Claim 24 wherein R^3 represents a cyclic, or part cyclic -C_{3-6}alkyl.

26. A compound for use as claimed in any one of Claims 1 to 25, wherein the condition is selected from rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerous colitis, multiple sclerosis, lymphoproliferative diseases (e.g. those caused by Epstein Barr virus and cytomegalovirus), rejection after

organ transplantation, Wegener' granulomatosus, psoriasis, Mb Bechterews, Behcets disease, Guillain Barre, dermatomyositis, myositis, polymyositis, primary biliary cirrhosis, anti-phospholipid syndrome, autoimmune hepatitis, autoimmune cardiomyopathy, alopecia areata, atherosclerosis, type 1 diabetes, autoimmune uveitis, Goodpasteure's syndrome, Graves' disease, Hashimotos disease, mixed connective tissue disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, Sjögren's syndrome, giant cell arteritis, ulcerative colitis, vasculitis, Churg–Strauss syndrome, postpolio syndrome, idiopathic thrombocytopenic purpura, Peyronie disease and Dupuytren's contracture.

27. A compound for use as claimed in Claim 26 wherein the condition is selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis, rejection after organ transplantation and atherosclerosis.

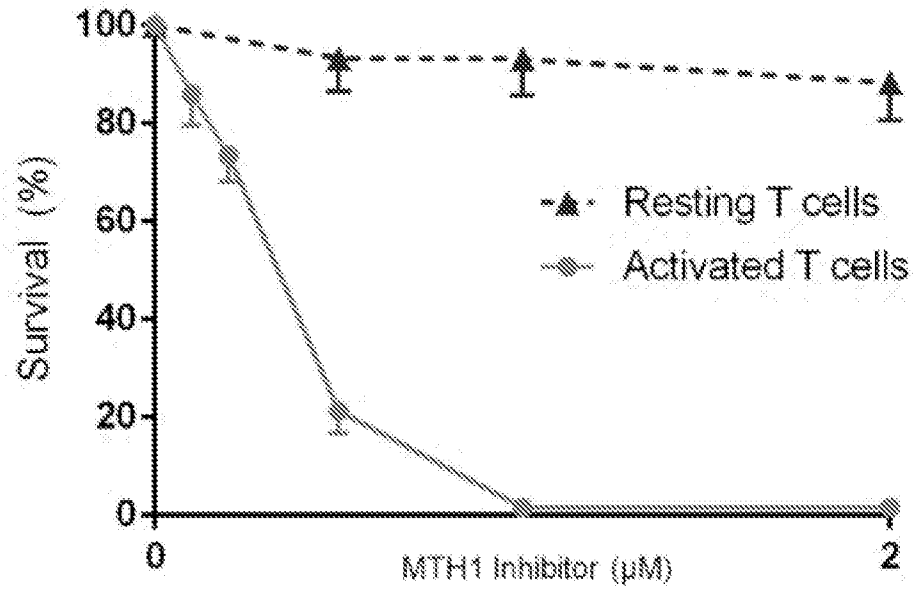
28. A compound for use as claimed in Claims 1 to 25, wherein the condition is psoriasis.

29. A combination product comprising:
(A) a compound for use as claimed in any one of Claims 1 to 28, or a pharmaceutically acceptable salt thereof; and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease as defined in any one of the Claims 1 to 28,
wherein each one of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

30. A combination product as claimed in Claim 29, wherein component (B) is selected from the group consisting of glucocorticoids, TNF-alpha inhibitors, anti-CD20, immunosupressants or antimetabolites.

31. A method of treatment of a disease as defined in any one of the Claims 1 to 28, which method comprises administration of a therapeutically effective amount of a compound as claimed in any one of Claims 1 to 28, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

Figure 1


100
80
60
40
20
0
Survival (%)
0
2
MTH1 Inhibitor (μM)
Resting T cells
Activated T cells