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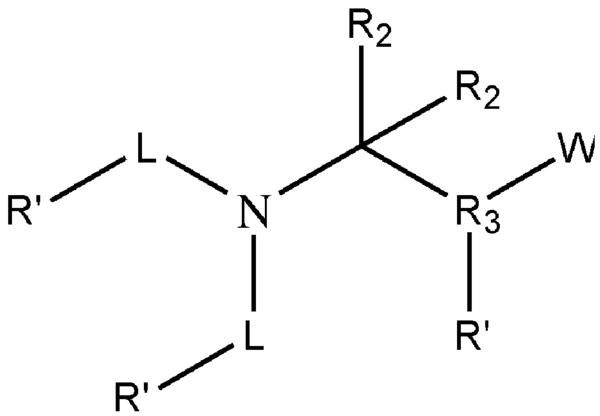
(54) **Title:** NOVEL HISTONE DEACETYLASE INHIBITORS



(57) Abstract: The present invention is a compound of the formula or a pharmaceutically acceptable salt thereof. The compounds are useful as HDAC inhibitors.

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NOVEL HISTONE DEACETYLASE INHIBITORS

Field of the Invention

The present invention relates to novel compounds which are inhibitors of histone deacetylase (HDAC) and therefore have therapeutic utility.

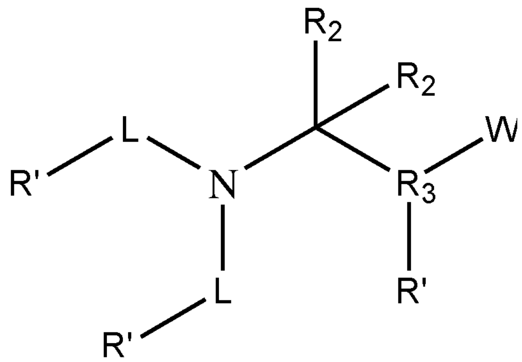
Background of the Invention

HDACs are zinc metalloenzymes that catalyse the hydrolysis of acetylated lysine residues. In histones, this returns lysines to their protonated state and is a global mechanism of eukaryotic transcriptional control, resulting in tight packaging of DNA in the nucleosome. Additionally, reversible lysine acetylation is an important regulatory process for non-histone proteins. Thus, compounds which are able to modulate HDAC have important therapeutic potential.

WO201 0/086646 discloses compounds which act as inhibitors of HDAC. The heteroaryl capping groups and the zinc-binding groups are joined via an alkylene linker.

Summary of the Invention

A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

each R' is independently selected from H and QRi;

each Q is independently selected from a bond, CO, $C0_2$, NH, S, SO, $S0_2$ or O;

each R_1 is independently selected from H, C_1-C_{10} alkyl, C_2-Ci_0 alkenyl, C_2-Cio alkynyl, aryl, heteroaryl, C_1-C_{10} cycloalkyl, halogen, C_1-C_{10} alkylaryl, C_1-C_{10} alkyl heteroaryl or C_1-C_{10} heterocycloalkyl;

each L is independently selected from a 5 to 10-membered nitrogen-containing heteroaryl;

W is a zinc-binding group;

each R_2 is independently hydrogen or C_1 to C_6 alkyl; and

R_3 is an aryl or heteroaryl;

each aryl or heteroaryl may be substituted by up to three substituents selected from C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl, bis(C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, $-S0_3H$, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl; and

each alkyl, alkenyl or alkynyl may be substituted with halogen, NH_2, $N0_2$ or hydroxyl.

These compounds have been surprisingly found to be potent HDAC inhibitors, which are highly selective for HDAC6 over HDAC1.

Description of the Invention

Definitions

As used herein, "alkyl" means a C_1-C_{10} alkyl group, which can be linear or branched. Preferably, it is a C_1-C_6 alkyl moiety. More preferably, it is a C_1-C_4 alkyl moiety. Examples include methyl, ethyl, n-propyl and t-butyl. It may be divalent, e.g. propylene.

As used herein, "cycloalkyl" contains from 3 to 10 carbon atoms. It may be monovalent or divalent.

As used herein, "alkenyl" means a C_2-Ci_0 alkenyl group. Preferably, it is a C_2-C_6 alkenyl group. More preferably, it is a C_2-C_4 alkenyl group. The alkenyl radicals may be mono- or di-saturated, more preferably monosaturated. Examples include vinyl, allyl, 1-propenyl, isopropenyl and 1-butenyl. It may be divalent, e.g. propenylene

As used herein, "alkynyl" is a C_2-C_{10} alkynyl group which can be linear or branched. Preferably, it is a C_2-C_4 alkynyl group or moiety. It may be divalent.

Each of the C_1-C_{10} alkyl, C_2-C_{10} alkenyl and C_2-C_{10} alkynyl groups may be optionally substituted with each other, i.e. C_1-C_{10} alkyl optionally substituted with C_2-Cio alkenyl. They may also be optionally substituted with aryl, cycloalkyl (preferably C_3-Cio), aryl or heteroaryl. They may also be substituted with halogen (e.g. F, Cl), NH_2, $N0_2$ or hydroxyl. Preferably, they may be substituted with up to 10 halogen atoms or more preferably up to 5 halogens. For example, they may be substituted by 1, 2, 3, 4 or 5 halogen atoms. Preferably, the halogen is fluorine. For example, C_1-C_10 alkyl may be CF_3, CHF_2, CH_2CF_3, CH_2CHF_2 or CF_2CF_3 or OCF_3, $OCHF_2$, OCH_2CF_3, OCH_2CHF_2 or OCF_2CF_3.

As used herein, "aryl" means a monocyclic, bicyclic, or tricyclic monovalent or divalent (as appropriate) aromatic radical, such as phenyl, biphenyl, naphthyl, anthracenyl, which can be optionally substituted with up to three substituents preferably selected from the group of C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl, bis(C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, -$S0_3H$, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

Amino means -NH_2.

As used herein, heteroaryl means a monocyclic, bicyclic or tricyclic monovalent or divalent (as appropriate) aromatic radical containing up to four heteroatoms selected from oxygen, nitrogen and sulfur, such as thiazolyl, tetrazolyl, imidazolyl, oxazolyl, isoxazolyl, thienyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, said radical being optionally substituted with up to three substituents preferably selected from the group of C_1-C_6 alkyl, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyl) amino C_1-C_3 alkyl, bis (C_1-C_3 alkyl) amino C_1-C_3 alkyl, C_1-C_3-acylamino, C_1-C_3 alkyl sulfonylamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyl aminocarbonyl, bis C_1-C_3 alkyl aminocarbonyl, -$S0_3H$, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyl aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

In the compounds of the invention, certain heteroaryl groups (i.e. L and R_3) are attached to R'. However, they may still be substituted by up to three additional substituents, selected from the groups defined above. Preferably, R' is the only substituent.

As used herein, the term heterocycle or heterocycloalkyl is a mono- or di-valent carbocyclic radical containing up to 4 heteroatoms selected from oxygen, nitrogen and sulfur. It may be bicyclic or monocyclic. It is preferably saturated. The word 'linker' has been used herein to mean di-valent. If the heterocycle is a di-valent linker, the heterocycle may be attached to neighbouring groups through a carbon atom, or through on of the heteroatoms, e.g. a N. Examples of heterocycles are piperazine and morpholine.

The heterocyclic ring may be mono- or di-unsaturated. The radical may be optionally substituted with up to three substituents independently selected from C_1-

C_6 alkyi, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyi, mono (C_1-C_3 alkyi) amino C_1-C_3 alkyi, bis (C_1-C_3 alkyi) amino C_1-C_3 alkyi, C_1-C_3-acylamino, C_1-C_3 alkyi sulfonylamino, halo e.g. F, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyi aminocarbonyl, bis C_1-C_3 alkyi aminocarbonyl, $-S0_3H$, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyi aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl.

As used herein, the above groups can be followed by the suffix -ene. This means that the group is divalent, i.e. a linker group.

As used herein, "thiol-protecting group" is typically:

(a) a protecting group that forms a thioether to protect a thiol group, for example a benzyl group which is optionally substituted by C_1-C_6 alkoxy (for example methoxy), C_1-C_6 acyloxy (for example acetoxy), hydroxy and nitro, picolyl, picolyl-N-oxide, anthryl methyl, diphenylmethyl, phenyl, t-butyl, adamantyl, C_1-C_6 acyloxymethyl (for example pivaloyloxymethyl, tertiary butoxycarbonyloxymethyl);

(b) a protecting group that forms a monothio, dithio or aminothioacetal to protect a thiol group, for example C_1-C_6 alkoxymethyl (for example methoxymethyl, isobutoxymethyl), tetrahydropyranyl, benzylthiomethyl, phenylthiomethyl, thiazolidine, acetamidemethyl, benzamidomethyl;

(c) a protecting group that forms a thioester to protect a thiol group, such as tertiary-butyloxycarbonyl (BOC), acetyl and its derivatives, benzoyl and its derivatives; or

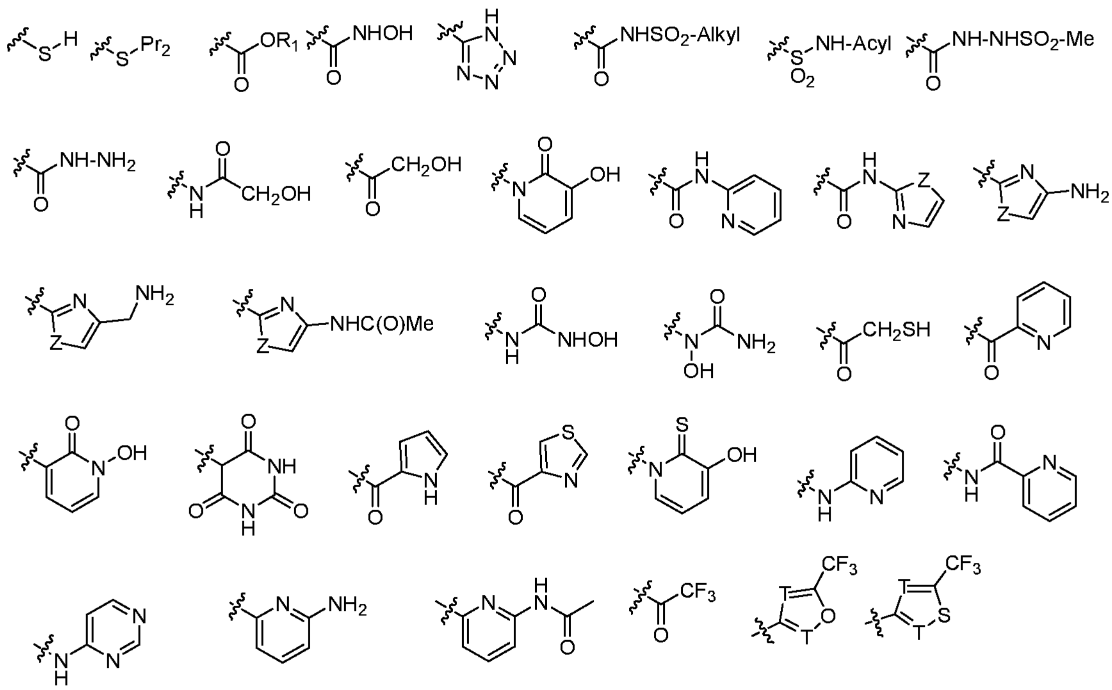
(d) a protecting group that forms a carbamic acid thioester to protect a thiol group, such as carbamoyl, phenylcarbamoyl, C_1-C_6 alkylcarbamoyl (for example methylcarbamoyl and ethylcarbamoyl).

Preferred groups of the invention

Preferably, at least one R_2 is H. Preferably, both R_2 groups are H.

The group W is a zinc-chelating residue, i.e. a metallophile capable of binding with zinc in the active site of HDAC. Suitable metallophiles are known to those skilled in the art.

In a preferred embodiment, W is selected from:



wherein R_1 is as defined in claim 1, Pr^2 is H or a thiol protecting group, Z is selected from O, S or NH and T is N or CH.

When W is $COOR_1$, preferably R_1 is not halogen. More preferably, when W is $COOR_1$, R_1 is H or C_1-C_{10} alkyl.

Preferably, W is -COOH, -CONHOH, CONHS0$_2$CH$_3$, -CONHNHS0$_2$CH$_3$, -CONHNH$_2$, -CONH(2-pyridyl), -NHCONHOH, tetrazole, hydroxypyridin-2-thione or hydroxypyridin-2-one. Preferably W is not $COOR_1$. More preferably, W is COOMe, -CONHOH, CONHSO2CH3, -CONHNHSO2CH3, -CONHNH2, -CONH(2-pyridyl) -NHCONHOH, tetrazole, hydroxypyridin-2-thione or hydroxypyridin-2-one. Even more preferably, W is -CONHOH, tetrazole, hydroxypyridin-2-thione or hydroxypyridin-2-one. Most preferably, W is -CONHOH.

In a preferred embodiment, in at least one, preferably both L groups, the atom that is directly bonded to X is a carbon, and at least one nitrogen atom is directly bonded to said carbon.

In an embodiment, at least one L group is a 5-membered heteroaryl. Preferably, at least one L group is a 6-membered heteroaryl. Even more preferably, both L groups are a 6-membered heteroaryl.

Preferably, at least one L group is pyridinyl, pyrimidinyl, pyridazinyl, oxadiazolyl, pyrazolyl, thiadiazolyl, pyrazinyl, benzofused thiazolyl, benzofused oxazolyl or benzofused imidazolyl. More preferably, at least one L group is pyridyl or pyrazinyl. Most preferably, one L is pyrazinyl and one L is pyridyl. Preferably, when L is pyridyl, it is substituted with a heteroaryl group. The heteroaryl group is preferably an optionally substituted (preferably substituted) pyridine.

Preferably, at least one L group is pyridinyl, oxadiazolyl, pyrazolyl, thiadiazolyl, pyrazinyl, benzofused thiazolyl, benzofused oxazolyl or benzofused imidazolyl.

Preferably, at least one L group is a 5 or 6-membered heteroaryl, which is optionally fused to a benzene.

Preferably, Q is a bond or O.

Preferably, R_3 is aryl. More preferably, R_3 is phenylene or phenylene substituted with a halogen.

Preferably, at least one, preferably both, R_2 is H.

In a preferred embodiment, at least one R' is H, halogen, CF_3, C_1-C_6 alkyl, aryl optionally substituted with halogen or heteroaryl optionally substituted with halogen. Preferably, the alkyl is substituted with at least one halogen, which is preferably fluorine.

In a preferred embodiment, the R' attached to R_3 is hydrogen or halogen. Preferably, R_3 is hydrogen or fluorine. More preferably, the R' attached to R_3 is hydrogen. In a preferred embodiment, at least one R', and preferably at least one of the R' that is attached to L, is H, C_1-C_{10} alkyl or O-(C_1-C_{10} alkyl). Preferably, at least one R' is substituted or unsubstituted aryl or 0-(substituted or unsubstituted aryl). Preferably, at least one R' is aryl or O-aryl, each of which may be substituted with a halogen, amino or C_1-C_{10} alkyl. The aryl may be substituted in any position. The aryl may be mono-, bis-, or tri-substituted.

In a preferred embodiment, at least one R', and preferably at least one of the R' that is attached to L, is H, C_1-C_{10} alkyl or O-(C_1-C_{10} alkyl), halogen, C_1-C_{10} heterocycloalkyl, aryl (preferably optionally substituted phenyl), trifluoromethyl or heteroaryl, preferably heteroaryl. Preferably, when R' is heteroaryl, it is optionally substituted pyridyl, preferably a substituted pyridyl.

In one embodiment, at least one R' that is attached to L is OCH_3 or CH_3. Preferably, at least one of the R' that is attached to L is heterocycloalkyl. Preferably, the heterocycloalkyl is morpholino.

In a preferred embodiment, when Q is a direct bond, R_1 is H, C_1-C_{10} alkyl or 0-(C $_1$-Cio alkyl), halogen (preferably F), C_1-C_{10} heterocycloalkyl (preferably morpholino), aryl (preferably optionally substituted phenyl), trifluoromethyl or heteroaryl, preferably heteroaryl. Preferably, when R_1 is heteroaryl, it is optionally substituted pyridyl, preferably a substituted pyridyl.

In a preferred embodiment, R_1 is C_1-C_{10} alkyl, C_2-Ci$_0$ alkenyl or C_2-Ci$_0$ alkynyl, preferably those groups are substituted with halogen, NH_2, N0 $_2$ or hydroxyl. More preferably, when R' or R_1 is C_1-C_{10} alkyl, it may be substituted with halogen which is preferably fluorine. The C_1-C_{10} alkyl group may be substituted by up to 10 halogen atoms or preferably, by up to 5 halogen atoms, i.e., 1, 2, 3, 4 or 5 halogen atoms. For example, R' or R_1 may be CF_3, CHF_2, CH_2CF_3, CH_2CHF_2 or CF_2CF_3 or OCFs, $OCHF_2$, OCH_2CF_3, OCH_2CHF_2 or OCF_2CF_3.

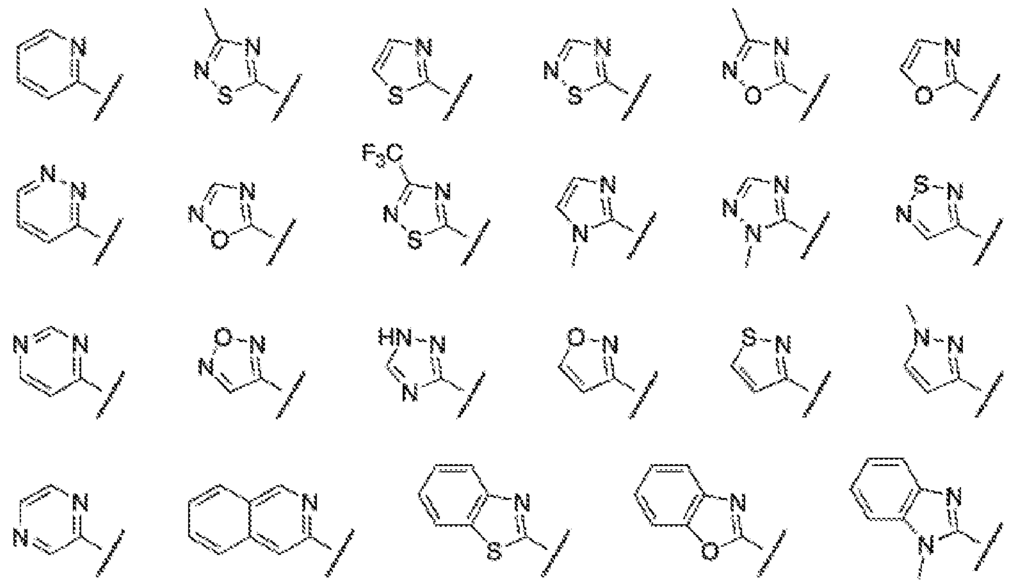
R' may be substituted onto any of the ring atoms of the L group or onto any of the ring atoms of the R_2 group.

Preferably, the L and R_3 groups have no other substitutions other than R'.

Preferably, Q is a direct bond.

Preferably, in addition to a N atom, L contains at least one other heteroatom in the heteroaryl ring which is selected from N, O or S.

In a preferred embodiment, L is:



In a preferred embodiment, L is a hydrogen bond-acceptor, and preferably not also a hydrogen bond donor. Preferably, L does not have a hydrogen atom attached to an electronegative atom, such as N or O.

The definition of hydrogen bond acceptors/donors is known to those skilled in the art. For example, a hydrogen bond donor will have a hydrogen attached to an electronegative atom, such as N or O. For example, a hydrogen bond acceptor will have a N or O, which has a free lone pair..

Preferably the atom of L that is directly bonded to the N atom of the formula of claim 1 is carbon, and at least one nitrogen atom is directly bonded to said carbon (preferably via a double bond). More preferably, said nitrogen atom is a hydrogen bond acceptor.

A pharmaceutical composition of the invention comprises a compound as defined above, and a pharmaceutically acceptable carrier or diluent. A pharmaceutical composition of the invention typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen-free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer. Preferably, the pharmaceutical composition comprises a pharmaceutically acceptable salt form of a compound of the invention.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulfonic, ethanesulfonic, ethanedisulfonic, salicylic, stearic, benzenesulfonic or p-toluenesulfonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aryl amines or heterocyclic amines.

For the avoidance of doubt, the present invention also embraces pro-drugs which react *in vivo* to give a compound of the present invention.

The compounds of the present invention are found to be inhibitors of HDAC. The compounds of the present invention are therefore therapeutically useful in the treatment of conditions affected by HDAC activity.

The compounds of the invention may be prepared by synthetic routes that will be apparent to those skilled in the art, e.g. based on the Examples.

The compounds of the present invention are found to be inhibitors of HDAC. The compounds of the present invention are therefore therapeutically useful.

The compounds of the invention and compositions comprising them may be administered in a variety of dosage forms. In one embodiment, a pharmaceutical composition comprising a compound of the invention may be formulated in a format suitable for oral, rectal, parenteral, intranasal or transdermal administration or administration by inhalation or by suppository. Typical routes of administration are parenteral, intranasal or transdermal administration or administration by inhalation.

The compounds of the invention can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

The compounds of the invention may also be administered by inhalation. An advantage of inhaled medications is their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed. A further advantage may be to treat diseases of the pulmonary system, such that delivering drugs by inhalation delivers them to the proximity of the cells which are required to be treated.

The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler.

The compounds of the invention may also be administered by intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. By this method absorption is very rapid and first pass metabolism is usually bypassed, thus reducing inter-patient variability. Further, the present invention also provides an intranasal device containing such a pharmaceutical composition.

The compounds of the invention may also be administered by transdermal administration. The present invention therefore also provides a transdermal patch containing a compound of the invention.

The compounds of the invention may also be administered by sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention.

A compound of the invention may also be formulated with an agent which reduces degradation of the substance by processes other than the normal metabolism of the patient, such as anti-bacterial agents, or inhibitors of protease enzymes which might be the present in the patient or in commensural or parasite organisms living on or within the patient, and which are capable of degrading the compound.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

In one embodiment the compounds of the present invention may be used in combination with another known inhibitor of HDAC, such as SAHA. In this embodiment, the combination product may be formulated such that it comprises each of the medicaments for simultaneous, separate or sequential use.

The compounds of the present invention can be used in both the treatment and prevention of cancer and can be used in a monotherapy or in a combination therapy. When used in a combination therapy, the compounds of the present invention are typically used together with small chemical compounds such as platinum complexes, anti-metabolites, DNA topoisomerase inhibitors, radiation, antibody-based therapies (for example herceptin and rituximab), anti-cancer vaccination, gene therapy, cellular therapies, hormone therapies or cytokine therapy.

In one embodiment of the invention a compound of the invention is used in combination with another chemotherapeutic or antineoplastic agent in the treatment of a cancer. Examples of such other chemotherapeutic or antineoplastic agents include platinum complexes including cisplatin and carboplatin, mitoxantrone, vinca alkaloids for example vincristine and vinblastine, anthracycline antibiotics for example daunorubicin and doxorubicin, alkylating agents for example chlorambucil and melphalan, taxanes for example paclitaxel, antifolates for example methotrexate and tomudex, epipodophyllotoxins for example etoposide, camptothecins for example irinotecan and its active metabolite SN38 and DNA methylation inhibitors for example the DNA methylation inhibitors disclosed in WO02/085400.

According to the invention, therefore, products are provided which contain a compound of the invention and another chemotherapeutic or antineoplastic agent as a combined preparation for simultaneous, separate or sequential use in alleviating a cancer. Also provided according to the invention is the use of compound of the invention in the manufacture of a medicament for use in the alleviation of cancer by co-administration with another chemotherapeutic or antineoplastic agent. The compound of the invention and the said other agent may be administrated in any order. In both these cases the compound of the invention and the other agent may be administered together or, if separately, in any order as determined by a physician.

HDAC is believed to contribute to the pathology and/or symptomology of several different diseases such that reduction of the activity of HDAC in a subject through inhibition of HDAC may be used to therapeutically address these disease states. Examples of various diseases that may be treated using the HDAC inhibitors of the present invention are described herein.

One set of indications that HDAC inhibitors of the present invention may be used to treat is those involving undesirable or uncontrolled cell proliferation. Such indications include benign tumours, various types of cancers such as primary tumours and tumour metastasis, restenosis (e.g. coronary, carotid, and cerebral lesions), abnormal stimulation of endothelial cells (atherosclerosis), insults to body tissue due to surgery, abnormal wound healing, abnormal angiogenesis, diseases that produce fibrosis of tissue, repetitive motion disorders, disorders of tissues that are not highly vascularized, and proliferative responses associated with organ transplants. More specific indications for HDAC inhibitors include, but are not limited to prostate cancer, lung cancer, acute leukaemia, multiple myeloma, bladder carcinoma, renal carcinoma, breast carcinoma, colorectal carcinoma, neuroblastoma and melanoma.

In one embodiment, a method is provided for treating diseases associated with undesired and uncontrolled cell proliferation. The method comprises administering to a subject suffering from uncontrolled cell proliferation a therapeutically effective amount of a HDAC inhibitor according to the present invention, such that said uncontrolled cell proliferation is reduced. The particular dosage of the inhibitor to be used will depend on the severity of the disease state, the route of administration, and related factors that can be determined by the attending physician. Generally, acceptable and effective daily doses are amounts sufficient to effectively slow or eliminate uncontrolled cell proliferation.

HDAC inhibitors according to the present invention may also be used in conjunction with other agents to inhibit undesirable and uncontrolled cell proliferation. Examples of other anti-cell proliferation agents that may be used in conjunction with the HDAC inhibitors of the present invention include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, Angiostatin™ protein, Endostatin™ protein, suramin, squalamine, tissue inhibitor of metalloproteinase-l, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1 , plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel, platelet factor 4, protamine sulfate (clupeine), sulfated chitin derivatives (prepared from queen crab shells), sulfated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((1-azetidine-2-carboxylic acid (LACA), cishydroxyproline, d,1-3,4-dehydroproline, thiaproline), beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomalate, d-penicillamine (CDPT), beta-1-anticollagenase-serum, alpha-2-antiplasmin, bisantrene, lobenzarit disodium, n-(2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide; angiostatic steroid, carboxyaminoimidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents that may be used include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: bFGF, aFGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2. Ferrara N. and Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

Generally, cells in benign tumours retain their differentiated features and do not divide in a completely uncontrolled manner. A benign tumour is usually localized and nonmetastatic. Specific types of benign tumours that can be treated using HDAC inhibitors of the present invention include hemangiomas, hepatocellular adenoma, cavernous haemangioma, focal nodular hyperplasia, acoustic neuromas, neurofibroma, bile duct adenoma, bile duct cystanoma, fibroma, lipomas, leiomyomas, mesotheliomas, teratomas, myxomas, nodular regenerative hyperplasia, trachomas and pyogenic granulomas.

In the case of malignant tumors, cells become undifferentiated, do not respond to the body's growth control signals, and multiply in an uncontrolled manner. Malignant tumors are invasive and capable of spreading to distant sites (metastasizing). Malignant tumors are generally divided into two categories: primary and secondary. Primary tumors arise directly from the tissue in which they are found. Secondary tumours, or metastases, are tumours that originated elsewhere in the body but have now spread to distant organs. Common routes for metastasis are direct growth into adjacent structures, spread through the vascular or lymphatic systems, and tracking along tissue planes and body spaces (peritoneal fluid, cerebrospinal fluid, etc.).

Specific types of cancers or malignant tumours, either primary or secondary, that can be treated using the HDAC inhibitors of the present invention include, but are not limited to, leukaemia, breast cancer, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, brain cancer, cancer of the larynx, gallbladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, colon, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumour, small-cell lung tumour, gallstones, islet cell tumour, primary brain tumour, acute and chronic lymphocytic and granulocytic tumours, hairy-cell tumour, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuromas, intestinal ganglioneuromas, hyperplastic corneal nerve tumour, marfanoid habitus tumour, Wilms' tumour, seminoma, ovarian tumour, leiomyomater tumour, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumour, polycythermia vera, adenocarcinoma, glioblastoma multiforme, leukemias, lymphomas, malignant melanomas, epidermoid carcinomas, and other carcinomas and sarcomas.

The HDAC inhibitors of the present invention may also be used to treat abnormal cell proliferation due to insults to body tissue during surgery. These insults may arise as a result of a variety of surgical procedures such as joint surgery, bowel surgery, and cheloid scarring. Diseases that produce fibrotic tissue that may be treated using the HDAC inhibitors of the present invention include emphysema. Repetitive motion disorders that may be treated using the present invention include carpal tunnel syndrome. An example of a cell proliferative disorder that may be treated using the invention is a bone tumour.

Proliferative responses associated with organ transplantation that may be treated using HDAC inhibitors of the invention include proliferative responses contributing to potential organ rejections or associated complications. Specifically, these proliferative responses may occur during transplantation of the heart, lung, liver, kidney, and other body organs or organ systems.

Abnormal angiogenesis that may be treated using this invention include those abnormal angiogenesis accompanying rheumatoid arthritis, ischemic-reperfusion related brain edema and injury, cortical ischemia, ovarian hyperplasia and hypervascularity, polycystic ovary syndrome, endometriosis, psoriasis, diabetic retinopathy, and other ocular angiogenic diseases such as retinopathy of prematurity (retrolental fibroplastic), macular degeneration, corneal graft rejection, neuroscular glaucoma and Oster Webber syndrome.

Examples of diseases associated with uncontrolled angiogenesis that may be treated according to the present invention include, but are not limited to retinal/choroidal neovascularization and corneal neovascularization. Examples of diseases which include some component of retinal/choroidal neovascularization include, but are not limited to, Best's diseases, myopia, optic pits, Stargart's diseases, Paget's disease, vein occlusion, artery occlusion, sickle cell anemia, sarcoid, syphilis, pseudoxanthoma elasticum carotid apo structive diseases, chronic uveitis/vitritis, mycobacterial infections, Lyme's disease, systemic lupus erythematosus, retinopathy of prematurity, Eale's disease, diabetic retinopathy, macular degeneration, Bechet's diseases, infections causing a retinitis or chroiditis, presumed ocular histoplasmosis, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma and post-laser complications, diseases associated with rubesis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy. Examples of corneal neovascularization include, but are not limited to, epidemic keratoconjunctivitis, Vitamin A deficiency, contact lens overwear, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phylectenulosis, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, polyarteritis, Wegener sarcoidosis, Scleritis, periphigoid radial keratotomy, neovascular glaucoma and retrolental fibroplasia, syphilis, Mycobacteria infections, lipid degeneration, chemical burns, bacterial ulcers, fungal ulcers, Herpes simplex infections, Herpes zoster infections, protozoan infections and Kaposi sarcoma.

Chronic inflammatory diseases associated with uncontrolled angiogenesis may also be treated using HDAC inhibitors of the present invention. Chronic inflammation depends on continuous formation of capillary sprouts to maintain an influx of inflammatory cells. The influx and presence of the inflammatory cells produce granulomas and thus maintains the chronic inflammatory state. Inhibition of angiogenesis using a HDAC inhibitor alone or in conjunction with other anti-inflammatory agents may prevent the formation of the granulosmas and thus alleviate the disease. Examples of chronic inflammatory diseases include, but are not limited to, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, and rheumatoid arthritis.

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are characterized by chronic inflammation and angiogenesis at various sites in the gastrointestinal tract. For example, Crohn's disease occurs as a chronic transmural inflammatory disease that most commonly affects the distal ileum and colon but may also occur in any part of the gastrointestinal tract from the mouth to the anus and perianal area. Patients with Crohn's disease generally have chronic diarrhoea associated with abdominal pain, fever, anorexia, weight loss and abdominal swelling. Ulcerative colitis is also a chronic, nonspecific, inflammatory and ulcerative disease arising in the colonic mucosa and is characterized by the presence of bloody diarrhoea. These inflammatory bowel diseases are generally caused by chronic granulomatous inflammation throughout the gastrointestinal tract, involving new capillary sprouts surrounded by a cylinder of inflammatory cells. Inhibition of angiogenesis by these inhibitors should inhibit the formation of the sprouts and prevent the formation of granulomas. Inflammatory bowel diseases also exhibit extra intestinal manifestations, such as skin lesions. Such lesions are characterized by inflammation and angiogenesis and can occur at many sites other the gastrointestinal tract. Inhibition of angiogenesis by HDAC inhibitors according to the present invention can reduce the influx of inflammatory cells and prevent lesion formation.

Sarcoidosis, another chronic inflammatory disease, is characterized as a multisystem granulomatous disorder. The granulomas of this disease can form anywhere in the body. Thus, the symptoms depend on the site of the granulomas and whether the disease is active. The granulomas are created by the angiogenic capillary sprouts providing a constant supply of inflammatory cells. By using HDAC inhibitors according to the present invention to inhibit angiogenesis, such granulomas formation can be inhibited. Psoriasis, also a chronic and recurrent inflammatory disease, is characterized by papules and plaques of various sizes. Treatment using these inhibitors alone or in conjunction with other anti-inflammatory agents should prevent the formation of new blood vessels necessary to maintain the characteristic lesions and provide the patient relief from the symptoms.

Rheumatoid arthritis (RA) is also a chronic inflammatory disease characterized by non-specific inflammation of the peripheral joints. It is believed that the blood vessels in the synovial lining of the joints undergo angiogenesis. In addition to forming new vascular networks, the endothelial cells release factors and reactive oxygen species that lead to pannus growth and cartilage destruction. The factors involved in angiogenesis may actively contribute to, and help maintain, the chronically inflamed state of rheumatoid arthritis. Treatment using HDAC inhibitors according to the present invention alone or in conjunction with other anti-RA agents may prevent the formation of new blood vessels necessary to maintain the chronic inflammation.

The compounds of the present invention can further be used in the treatment of cardiac/vasculature diseases such as hypertrophy, hypertension, myocardial infarction, reperfusion, ischaemic heart disease, angina, arrhythmias, hypercholesterolemia, atherosclerosis and stroke. The compounds can further be used to treat neurodegenerative disorders/CNS disorders such as acute and chronic neurological diseases, including stroke, Huntington's disease, Amyotrophic Lateral Sclerosis and Alzheimer's disease.

The compounds of the present invention can also be used as antimicrobial agents, for example antibacterial agents. The invention therefore also provides a compound for use in the treatment of a bacterial infection. The compounds of the present invention can be used as anti-infectious compounds against viral, bacterial, fungal and parasitic infections. Examples of infections include protozoal parasitic infections (including Plasmodium, Cryptosporidium parvum, toxoplasma gondii, sarcocystis neurona and Eimeria sp.)

The compounds of the present invention are particularly suitable for the treatment of undesirable or uncontrolled cell proliferation, preferably for the treatment of benign tumours/hyperplasias and malignant tumours, more preferably for the treatment of malignant tumours and most preferably for the treatment of chronic lymphocytic leukaemia (CLL), breast cancer, prostate cancer, ovarian cancer, mesothelioma, T-cell lymphoma.

In a preferred embodiment of the invention, the compounds of the invention are used to alleviate cancer, cardiac hypertrophy, chronic heart failure, an inflammatory condition, a cardiovascular disease, a haemoglobinopathy, a thalassemia, a sickle cell disease, a CNS disorder, an autoimmune disease, organ transplant rejection, diabetes, osteoporosis, MDS, benign prostatic hyperplasia, oral leukoplakia, a genentically related metabolic disorder, an infection, Rubens-Taybi, fragile X syndrome, or alpha-1 antitrypsin deficiency, or to accelerate wound healing, to protect hair follicles or as an immunosuppressant.

Typically, said inflammatory condition is a skin inflammatory condition (for example psoriasis, acne and eczema), asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), Crohn's disease or colitis.

Typically, said cancer is chronic lymphocytic leukaemia, breast cancer, prostate cancer, ovarian cancer, mesothelioma or T-cell lymphoma.

Typically, said cardiovascular disease is hypertension, myocardial infarction (MI), ischemic heart disease (IHD) (reperfusion), angina pectoris, arrhythmia, hypercholesterolemia, hyperlipidaemia, atherosclerosis, stroke, myocarditis, congestive heart failure, primary and secondary i.e. dilated (congestive) cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, peripheral vascular disease, tachycardia, high blood pressure or thrombosis.

Typically, said genentically related metabolic disorder is cystic fibrosis (CF), peroxisome biogenesis disorder or adrenoleukodystrophy.

Typically, the compounds of the invention are used as an immunosuppressant following organ transplant.

Typically, said infection is a viral, bacterial, fungal or parasitic infection, in particular an infection by S aureus, P acne, Candida or aspergillus.

Typically, said CNS disorder is Huntingdon's disease, Alzheimer's disease, multiple sclerosis or amyotrophic lateral sclerosis.

In this embodiment, the compounds of the invention may be used to alleviate cancer, cardiac hypertrophy, chronic heart failure, an inflammatory condition, a cardiovascular disease, a haemoglobinopathy, a thalassemia, a sickle cell disease, a CNS disorder, an autoimmune disease, diabetes or osteoporosis, or are used as an immunosuppressant.

The compounds of the invention may also be used to alleviate chronic lymphocytic leukaemia (CLL), breast cancer, prostate cancer, ovarian cancer, mesothelioma, T-cell lymphoma, cardiac hypertrophy, chronic heart failure or a skin inflammatory condition, in particular psoriasis, acne or eczema.

The compounds of the present invention can be used in the treatment of animals, preferably in the treatment of mammals and more preferably in the treatment of humans.

The compounds of the invention may, where appropriate, be used prophylactically to reduce the incidence of such conditions.

In use, a therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration.

Compounds of the invention may be tested for HDAC inhibitory activity by any suitable assay, e.g. the assay described in WO2008/062201 .

The following Examples illustrate the invention.

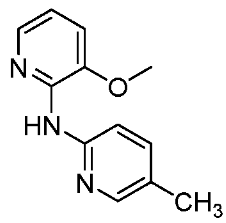
General methods

i. General Procedure for Synthesis of Secondary Amines

Method A (Using BINAP): 4,6-Dimethylpyridin-2-amine (200mg, 1.63mmol), 2-bromo-5-fluoropyridine (317mg, 1.8mmol), potassium ferf-butoxide (236mg, 2.45mmol) and (±)-BINAP (40mg, 0.06mmol) were stirred in toluene (4ml_) and degassed using Ar(g) for 30 min. $Pd_2(dba)_3$ (45mg, 0.049mmol) was then added and the reaction mixture stirred for 12h at 90°C under Ar(g). The reaction was monitored by TLC. Following complete consumption of starting material, the reaction mixture was diluted with CH_2Cl_2 (20ml_) and silica was added. The solvent was removed *in vacuo* and the resulting dry loaded material was purified by silica gel column chromatography with hexane/EtOAc (4:1-1:1), to provide N-(5-fluoropyridin-2-yl)-4,6-dimethylpyridin-2-amine.

Method B (Using SPhos): 2-Bromopyridine (200mg, 1.26mmol), 5-methylpyridin-2-amine (150mg, 1.38mmol), potassium ferf-butoxide (182mg, 1.89mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (20mg, 0.05mmol) were stirred in toluene (4ml_) and the reaction mixture was degassed using Ar(g) for 30 min. $Pd_2(dba)_3$ (34mg, 0.037mmol) was then added, and the reaction mixture was stirred for 12h at 90°C under Ar(g). The reaction was monitored by TLC. Following complete consumption of the starting material, the reaction mixture was diluted with CH_2Cl_2 (20ml_) and silica was added. The solvent was removed *in vacuo,* and the resulting dry loaded material was purified by silica gel column chromatography with hexane/EtOAc,(4:1-1:1), to provide N-(pyridin-2-yl)-5-methylpyridin-2-amine.

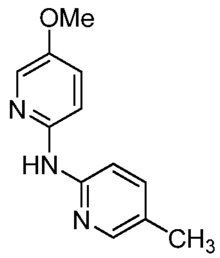
a) 3-Methoxy-N-(5-methylpyridin-2-yl)pyridin-2-amine



Synthesised according to the general procedure Method B (Using SPhos).

^1H NMR (400 MHz, Chloroform-d), δ_H ppm: 8.44 (d, *J*=8.6 Hz, 1H), 8.02-8.13 (m, 1H), 7.73-7.93 (m, 2H), 7.48 (dd, J^8.6, 2.3 Hz, 1H), 6.99 (dd, J^7.8, 1.5 Hz, 1H), 6.83-6.71 (m, 1H), 3.89 (s, 3H), 2.27 (s, 3H).

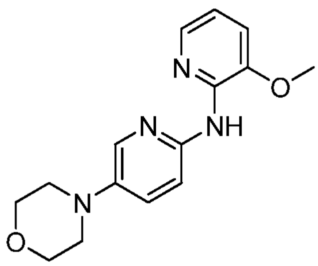
b) 5-Methoxy-N-(5-methylpyridin-2-yl)pyridin-2-amine



Synthesised according to the general procedure Method B (Using SPhos).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.04 (d, *J=2.5* Hz, 1H), 7.95 (d, *J*=3.0 Hz, 1H), 7.50 (d, *J*=9.0 Hz, 1H), 7.40 (dd, J^8.4, 2.6 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 1H), 7.22 (dd, J^9.0, 3.1 Hz, 1H), 3.87 (m, 3H), 2.25 (s, 3H).

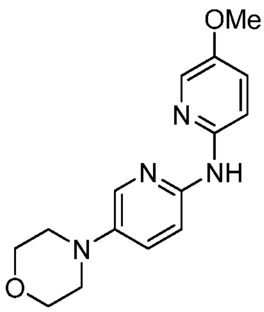
c) 3-Methoxy-N-(5-morpholinopyridin-2-yl)pyridin-2-amine



Synthesised according to the general procedure Method B (Using SPhos).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.45 (d, *J*=9.1 Hz, 1H), 7.94 (d, *J*=3.0 Hz, 1H), 7.83 (dd, ^=5.1 , 1.5 Hz, 1H), 7.31 (dd, ^=9.1 , 3.1 Hz, 1H), 6.98 (dd, J^7.9, 1.5 Hz, 1H), 6.73 (dd, J^7.8, 5.1 Hz, 1H), 3.76-3.98 (m, 7H), 3.06-3.16 (m, 4H).

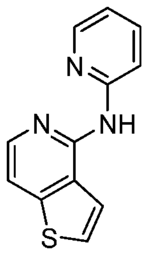
d) 5-Methoxy-N-(5-morpholinopyridin-2-yl)pyridin-2-amine



Synthesised according to the general procedure Method B (Using SPhos).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 7.90 (dd, ^=15.8, 3.0 Hz, 2H), 7.43 (d, *J*=9.0 Hz, 2H), 7.19-7.30 (m, 2H), 3.87 (t, *J=4.8* Hz, 4H), 3.82 (s, 3H), 3.00-3.16 (m, 4H).

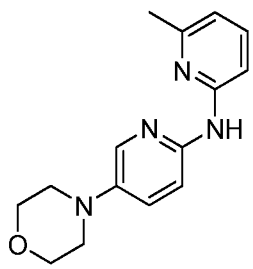
e) N-(Pyridin-2-yl)thieno[3,2-c]pyridin-4-amine



Synthesised according to the general procedure Method B (Using SPhos).

^{1}H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.58 (d, J=8.4 Hz, 1H), 8.26 (dd, ^=5.1, 2.0 Hz, 1H), 8.12 (d, J=5.7 Hz, 1H), 7.72 (ddd, J^8.8, 7.1, 1.9 Hz, 1H), 7.51 (d, J=5.9 Hz, 1H), 7.46 (d, J=5.4 Hz, 1H), 7.38 (d, J=5.7 Hz, 1H), 6.93 (ddd, J=7.1, 4.8, 1.0 Hz, 1H).

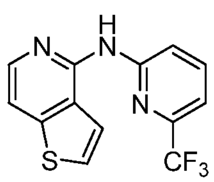
f) 6-Methyl-N-(5-morpholinopyridin-2-yl)pyridin-2-amine



Synthesised according to the general procedure Method B (Using SPhos).

^{1}H NMR (400 MHz, Chloroform-cO, δ_H ppm: 7.94 (d, J=3.0 Hz, 1H), 7.40-7.59 (m, 2H), 7.24 (d, J=8.1 Hz, 2H), 6.66 (d, J=7.3 Hz, 1H), 3.80-3.96 (m, 4H), 3.01-3.17 (m, 4H), 2.45 (s, 3H).

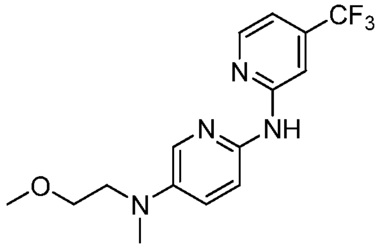
g) N-(6-(Trifluoromethyl)pyridin-2-yl)thieno[3,2-c]pyridin-4-amine



Synthesised according to the general procedure Method A (Using BINAP).

^{1}H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.82 (d, J=8.5 Hz, 1H), 8.14 (d, J=5.7 Hz, 1H), 7.83 (dd, ^=18.3, 10.3 Hz, 2H), 7.51 (s, 1H), 7.44 (d, J=5.7 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H).

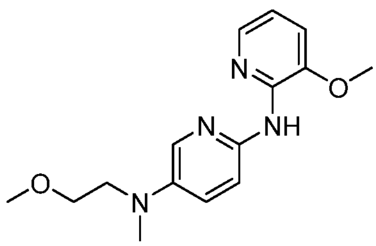
h) N5-(2-Methoxyethyl)-N5-methyl-N2-(4-(trifluoromethyl)pyridin-2-yl)pyridine-2,5-diamine



Synthesised according to the general procedure Method A (Using BINAP).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.32 (d, *J*=5.2 Hz, 1H), 7.87 (d, J=3.1 Hz, 1H), 7.70-7.78 (m, 1H), 7.29-7.37 (m, 1H), 7.15 (dd, J^9.0, 3.1 Hz, 1H), 6.88-6.98 (m, 1H), 3.54-3.59 (m, 2H), 3.48 (t, *J*=5.5 Hz, 2H), 3.37 (s, 3H), 2.98 (s, 3H).

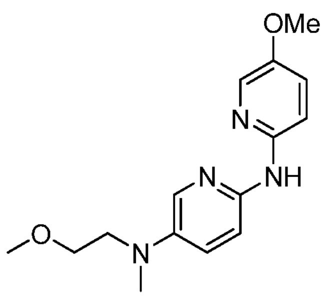
i) N5-(2-Methoxyethyl)-N2-(3-methoxypyridin-2-yl)-N5-methylpyridine-2,5-diamine



Synthesised according to the general procedure Method B (Using SPhos).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 8.37 (d, *J*=9.1 Hz, 1H), 7.81 (q, *J*=1.7 Hz, 2H), 7.19 (dd, ^=9.1 , 3.1 Hz, 1H), 6.96 (dd, J^7.7, 1.5 Hz, 1H), 6.70 (dd, J^7.8, 5.1 Hz, 1H), 3.88 (s, 3H), 3.56 (t, *J*=5.8 Hz, 2H), 3.45 (t, *J*=5.8 Hz, 2H), 3.36 (s, 3H), 2.96 (s, 3H).

j) N5-(2-methoxyethyl)-N2-(5-methoxypyridin-2-yl)-N5-methylpyridine-2,5-diamine



Synthesised according to the general procedure Method B (Using SPhos).

[1]H NMR (400 MHz, Chloroform-cO, δ_H ppm: 7.89 (d, *J*=3.0 Hz, 1H), 7.74 (d, *J=ZA* Hz, 1H), 7.45 (d, *J*=*9.*1 Hz, 1H), 7.37 (d, *J*=9.0 Hz, 1H), 7.19 (ddd, ^=12.0, 9.0, 3.1 Hz, 2H), 3.82 (s, 3H), 3.55 (t, *J*=5.8 Hz, 2H), 3.43 (t, *J*=5.8 Hz, 2H), 3.36 (s, 3H), 2.94 (s, 3H).

iii. General Procedure for Alkylation and Hydroxamic Acid Formation

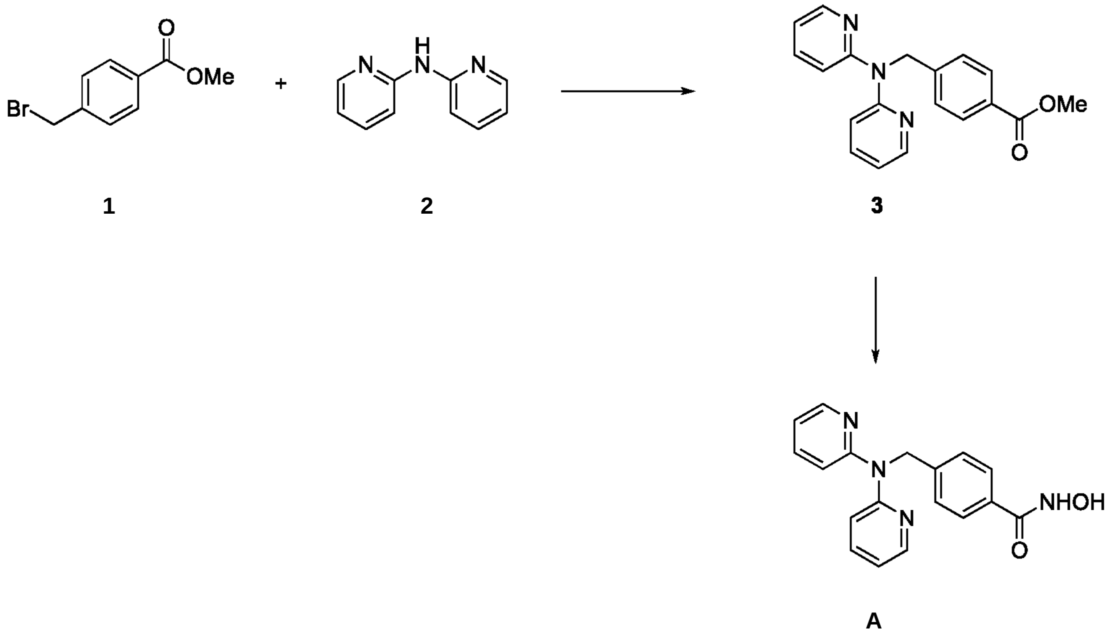
NaH (12mg, 0.5mmol, 2eq) was added portion-wise to secondary amine (50mg, 0.25mmol, 1eq) in DMF (2mL) at 0°C under Ar(g). Following addition, the reaction mixture was stirred for 20min, then methyl-4-(bromomethyl)benzoate (57mg, 0.25mmol, 1eq) was added. The reaction mixture was stirred at rt under Ar(g) for 2h, and the reaction was monitored by TLC. Following complete consumption of the starting material, the reaction mixture was poured onto brine (25ml_), extracted with EtOAc (3 x 25ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting crude product was purified by silica gel column chromatography with hexane/EtOAc (19:1-3:1), to provide the desired methyl ester as a gummy, yellowish solid.

To a stirred solution of the methyl ester (70mg, 0.20mmol) in MeOH/CH_2Cl_2 (3:1 , 4ml_) under an inert atmosphere was added 50% aq. hydroxylamine sol (2.5ml_) at 0°C, and the resulting reaction mixture was stirred for 20min. Sodium hydroxide solution (54mg in 1ml_ water, 1.35mmol) was then added to the reaction mixture; this was following by stirring for 30min, and the mixture was then warmed to rt and stirred for 2h. The reaction was monitored by TLC. Following complete consumption of the starting material, the volatiles were concentrated *in vacuo.* The residue was acidified with acetic acid to pH~6. The compound was extracted with CH_2Cl_2/MeOH (9:1) (3 x 20mL); the combined organic extracts were concentrated *in vacuo* to obtain the crude product, which was purified by silica gel column chromatography (1-10% MeOH/CH_2Cl_2) to afford the desired product as gummy, yellowish solid.

Specific Examples

Example A

4-{[Bis(pyridin-2-yl)amino]methyl}-N-hydroxybenzamide

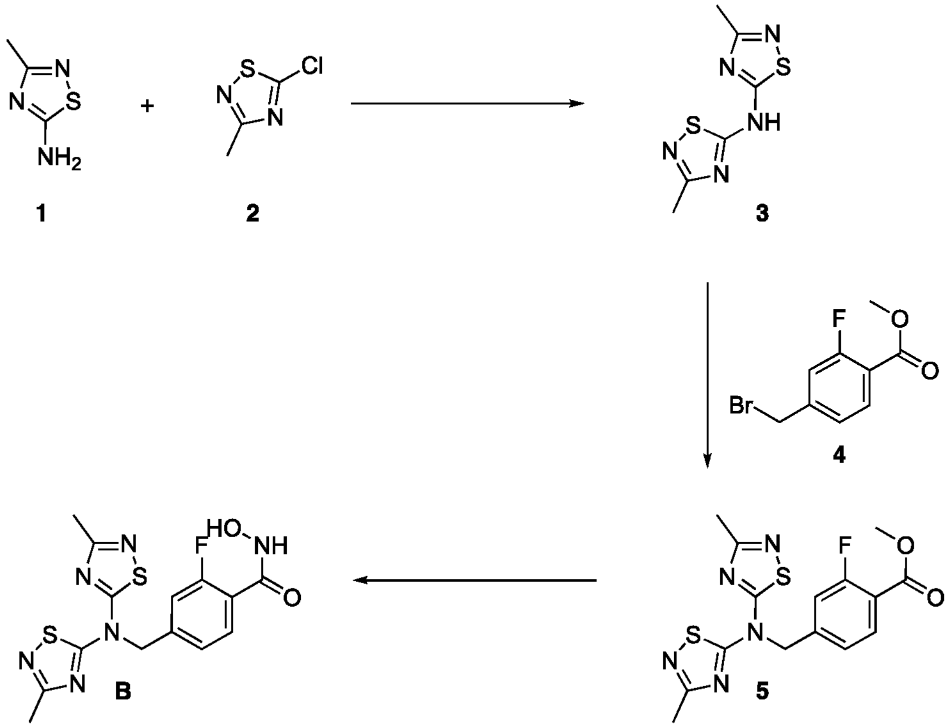


NaH (83mg, 2.18mmol) was added to 2,2'-dipyridylamine, **2** (373mg, 2.18mmol) in DMF (5mL) at rt. After 15 min, methyl-4-(bromomethyl)benzoate **(1)** (500mg, 2.18mmol) was added, and the reaction mixture was subsequently stirred at 90˚C for 1h under Ar(g). Once cooled to rt, the reaction mixture was poured onto brine (50ml_) and extracted twice with EtOAc (2 x 25ml_). The organic phases were combined, dried over $MgS0_4$, filtered, and subsequently concentrated *in vacuo.* The resulting residue was purified by silica gel column chromatography with hexanes/EtOAc (4:1) to furnish **3** as a white solid (429mg, 62%).
LCMS (ES): found 319.9 $[M+H]^+$.

A freshly prepared solution of NH_2OH in MeOH (0.4M, 20ml_) was added to 4-{[bis(pyridin-2-yl)amino]methyl}benzoate **(3)** (100mg, 0.3mmol) at 0˚C followed by KOH solubilized in MeOH (0.8M, 4ml_). The reaction mixture was then stirred at rt for 18h, was subsequently concentrated *in vacuo (ca* 5ml_) and poured onto water (50ml_). The basic aqueous phase was extracted initially with EtOAc (25ml_) and the phases were separated. The aqueous was then neutralized with 2N HCl and extracted again with EtOAc (25ml_). The resulting organic phase was dried over $MgS0_4$, filtered and subsequently concentrated *in vacuo* to provide **Example A** as a white solid (51 mg, 51%).
^{1}H NMR (400 MHz, Methanol-^), δ_H ppm: 6.69-6.76 (m, 2H), 6.07-6.15 (m, 4H), 5.91 (d, J=8.6 Hz, 2H), 5.65 (d, J=8.1 Hz, 2H), 5.44 (dd, J=6.6, 5.1 Hz, 2H), 3.97 (s, 2H).
LCMS (ES): found 321.1 $[M+H]^+$.

Example B

4-{[Bis(3-methyl-1,2,4-thiadiazol-5-yl)amino]methyl}-2-fluoro-N-hydroxybenzamide



NaH (60% in oil) (50mg) was added to a solution of 3-methyl-1 ,2,4-thiadiazol-5-amine **(1)** (115mg, 1mmol) in NMP (2ml_). After 10min, 5-chloro-3-methyl- 1,2,4-thiadiazole **(2)** (140mg, 1.05mmol) was added and the resultant mixture stirred at 45°C under N_2(g). After 4h, the reaction mixture was diluted with EtOAc and extracted with saturated bicarbonate solution (x3). Analysis indicated that all desired product was in the aqueous phase. The combined aqueous phases were concentrated to dryness; the resultant residue was slurried with MeCN (2 x 100ml_) and filtered. The filtrate was concentrated to afford (3) as an oil / NMP solution (700mg).

LCMS (ES): found 214.0 $[M+H]^+$.

Potassium carbonate (360mg) and methyl 4-(bromomethyl)-2-fluorobenzoate **(4)** (160mg, 0.65mmol) were added to a solution of 3-methyl-N-(3-methyl-1,2,4-thiadiazol-5-yl)-1 ,2,4-thiadiazol-5-amine (3) (<1mmol) in MeCN (10ml_) and the reaction mixture was heated, under N_2(g), with stirring, at 50°C. After 2h, the reaction mixture was cooled, diluted with EtOAc and extracted sequentially with water, saturated bicarbonate solution and saturated brine solution, and was then

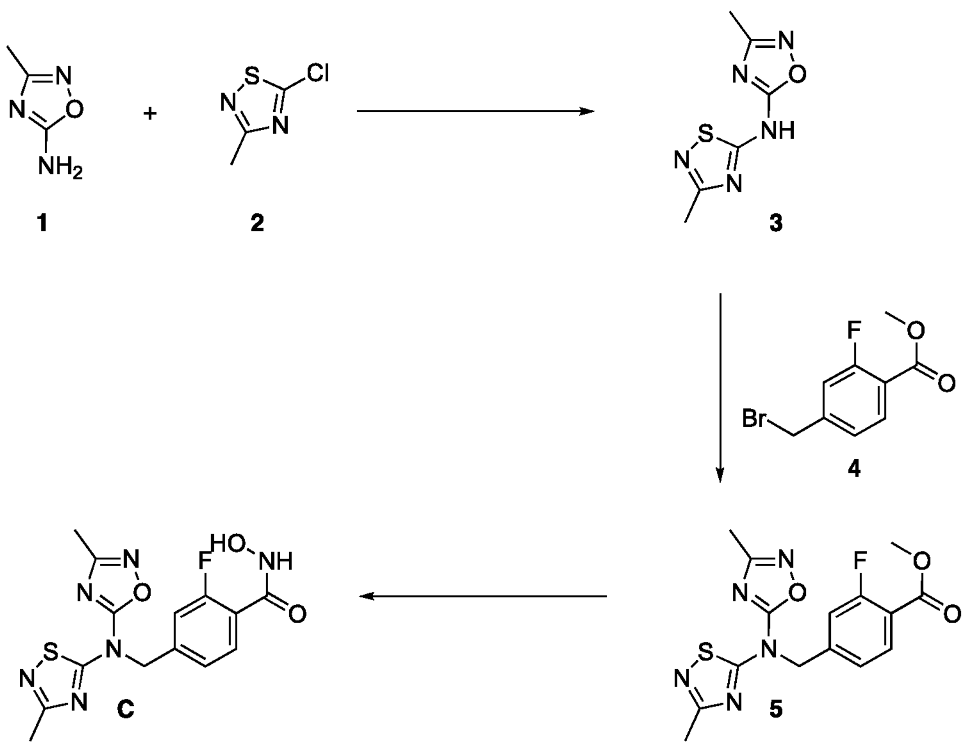
dried over Na_2SO_4, filtered and concentrated. Purification on silica with CH_2Cl_2/MeOH (1:0-97:3) yielded **(5)** as a solid (180mg, 73%).
LCMS (ES): found 380.0 $[M+H]^+$.

50% Hydroxylamine aqueous solution (2ml_) was added to a solution of methyl 4-{[bis(3-methyl-1 ,2,4-thiadiazol-5-yl)amino]methyl}-2-fluorobenzoate **(5)** (180mg, 0.47mmol) in MeOH (8mL). The solution was stirred at 45°C for 7 days, sealed in a vial. The resulting reaction mixture became heterogeneous; on cooling, a white solid was collected by filtration, washed with cold methanol and dried *in vacuo* to afford the title product, **Example B**, as solid (50mg, 28%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 10.90 (br. s., 1H), 9.17 (br. s., 1H), 7.51 (t, J=7.6 Hz, 1H), 7.27 (d, J=10.8 Hz, 1H), 7.16 (dd, J=7.9, 1.3 Hz, 1H), 5.57 (s, 2H), 2.50 (s, 6H).
LCMS (ES): found 381 .0 $[M+H]^+$.

Example C

2-Fluoro-N-hydroxy-4-{[(3-methyl-1,2,4-oxadiazol-5-yl)(3-methyl-1 ,2,4-thiadiazol-5-yl)amino]methyl}benzamide



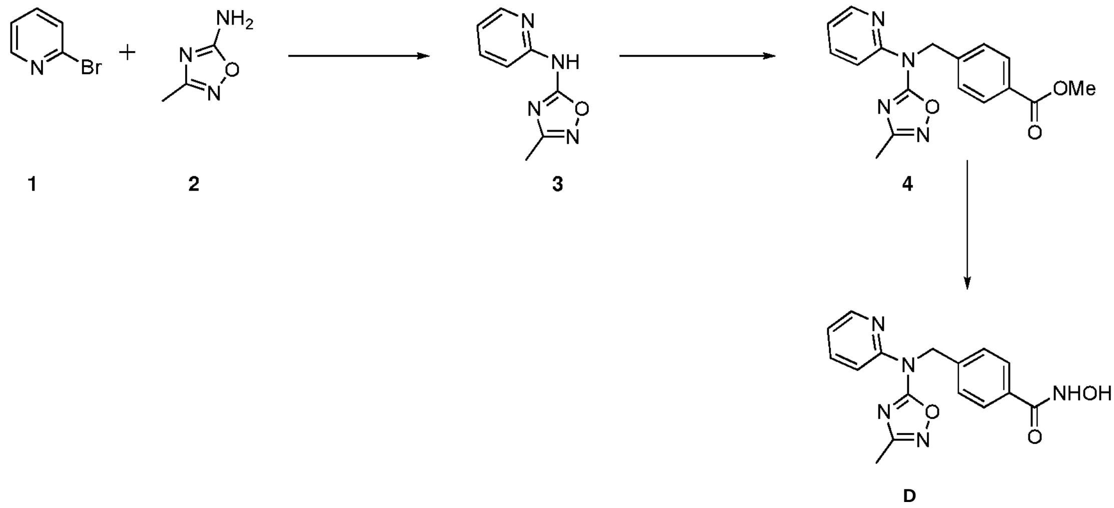
NaH (60% in oil) (50mg) was added to a solution of 3-methyl-1 ,2,4-oxadiazol-5-amine **(1)** (100mg, 1mmol) in NMP (2ml_). After 10min, 5-chloro-3-methyl-1,2,4-

thiadiazole **(2)** (150mg, 1.1 mmol) was added, and the resultant mixture was stirred at 45°C under N_2(g). After 18h, analysis by LCMS was conducted.
LCMS (ES): found 198.0 $[M+H]^+$.

NaH (60% in oil) (70mg) and methyl 4-(bromomethyl)-2-fluorobenzoate **(4)** (200mg, 0.81 mmol) were added to the above reaction mixture and heating was continued at 45°C under N_2(g). After 3h, a further quantity of **(4)** (90mg, 0.36mmol) was added. After an additional 2h, the reaction mixture was cooled, diluted with EtOAc, and extracted sequentially with water saturated bicarbonate solution (x2), and was then dried over Na_2S0_4, filtered and concentrated. Purification by silica gel chromatography with CH_2Cl_2/MeOH (1:0-97:3) yielded a residue **(5)** (350mg, 96% over 2 steps).
LCMS (ES): found 364.0 $[M+H]^+$.

50% Hydroxylamine aqueous solution (1ml_) was added to a crude solution of methyl 4-{[bis(3-methyl-1 ,2,4-thiadiazol-5-yl)amino]methyl}-2-fluorobenzoate **(5)** (350mg, 0.96mmol) in methanol (5ml_). The resulting solution was stirred at 45-50°C for 5 days, sealed in a vial. The reaction mixture turned heterogeneous and, on cooling, a white solid was filtered off and the resulting filtrate was concentrated. The filtrate was purified by RP-HPLC on Xterra 10-70% MeCN/water + 0.1% formic acid, to furnish the title compound, **Example C** (30mg, 8%).
^{1}H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 7.69 (t, J=7.6 Hz, 1H), 7.12-7.22 (m, 2H), 5.48 (s, 2H), 2.44 (s, 3H), 2.32 (s, 3H).
LCMS (ES): found 365.0 $[M+H]^+$.

Example D
N-Hydroxy-4-(((3-methyl-1,2,4-oxadiazol-5-yl)(pyridin-2-yl)amino)methyl)benzamide



2-Bromopyridine **(1)** (1.0g, 6.32mmol), 3-methyl-1,2,4-oxadiazol-5-amine **(2)** (0.940g, 9.49mmol), Xantphos (0.366g, 0.63mmol), and Cs_2C0_3 (4.1g, 12.64mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.28g, 0.31 mmol) was then added to the reaction mixture, which was heated at 90°C for 30h. It was then poured into demineralized water (200ml_) and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide 3-methyl-N-(pyridin-2-yl)-1 , 2, 4-oxadiazol-5-amine **(3)** as a white solid (0.7g, 63%).

LCMS (ES): Found 177.1 $[M+H]^+$.

NaH (60%) (52.5mg, 1.31 mmol) was added portion-wise to 3-methyl-N-(pyridin-2-yl)-1 ,2,4-oxadiazol-5-amine **(3)** (220mg,1.25mmol) in DMF (5ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (372mg, 1.62mmol) was added, and stirring was continued at 80°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to furnish methyl 4-(((3-methyl-1,2,4-oxadiazol-5-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** as a white solid (130mg, 40%).

LCMS (ES): Found 325.1 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (0.91 g, 16.3mmol) in MeOH (10ml_) was added to $NH_2OH.HCl$ (1.12g, 16.3mmol) in MeOH (10ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts;

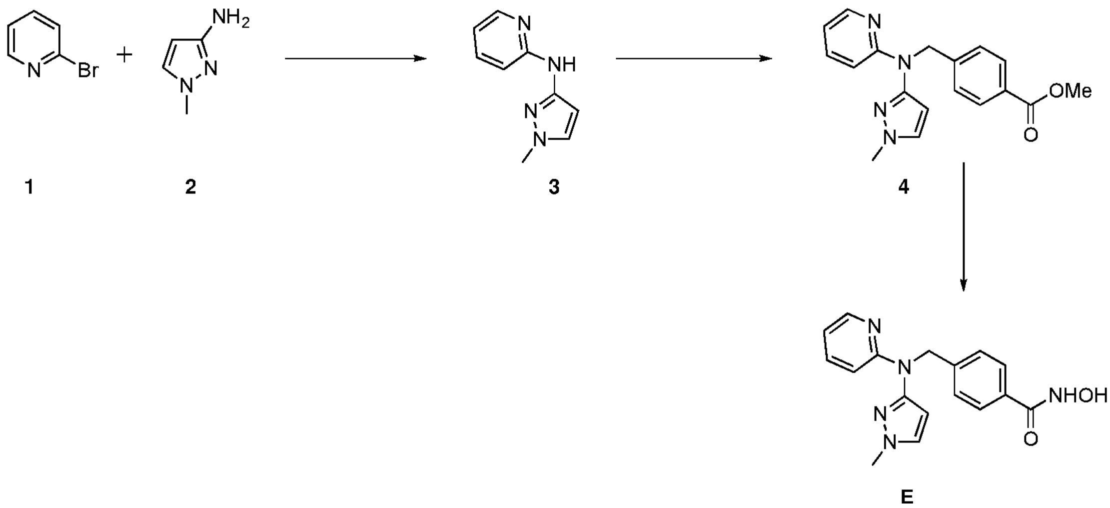
it was then added to methyl 4-(((3-methyl-1,2,4-oxadiazol-5-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** (105.5mg, 0.3mmol) followed by KOH (181mg, 3.2mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (15ml_/35mL), and extracted with CH_2Cl_2 (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated in vacuo. The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (10:90) to provide N-hydroxy-8-((3-methyl-1,2,4-oxadiazol-5-yl)(pyridin-2-yl)amino)octanamide, **Example D,** as a light yellow solid (12.2mg, 40%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.14 (br. s., 1H), 9.01 (br. s., 1H), 8.42 (dd, J=4.8, 1.1 Hz, 1H), 8.07 (d, J=8.4 Hz, 1H), 7.92 (ddd, J=8.5, 7.4, 2.0 Hz, 1H), 7.66 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 7.23 (ddd, J=7.3, 4.9, 0.8 Hz, 1H), 5.48 (s, 2H), 2.23 (s, 3H).

LCMS (ES): Found 326.1 $[M+H]^+$.

Example E

N-Hydroxy-4-(((1-methyl-1H-pyrazol-3-yl)(pyridin-2-yl)amino)methyl)benzamide



2-Bromopyridine **(1)** (1.0g, 6.3mmol), 1-methyl-1 H-pyrazol-3-amine **(2)** (0.79g, 8.2mmol), Xantphos (0.37g, 0.63mmol), and Cs_2C0_3 (4.1g, 12.6mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was then degassed with N_2(g), and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.29g, 0.31mmol) was added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(1-methyl-1 H-pyrazol-3-yl)pyridin-2-amine **(3)** as a yellow solid (0.75g, 68%).

LCMS (ES): Found 175.2 $[M+H]^+$.

NaH (60%) (60.4mg, 1.5mmol) was added portion-wise to N-(1-methyl-1H-pyrazol-3-yl)pyridin-2-amine **(3)** (250mg,1.4mmol) in DMF (8ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (428mg, 1.8mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((1-methyl-1H-pyrazol-3-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (440mg, 82%).

LCMS (ES): Found 323.1 $[M+H]^+$.

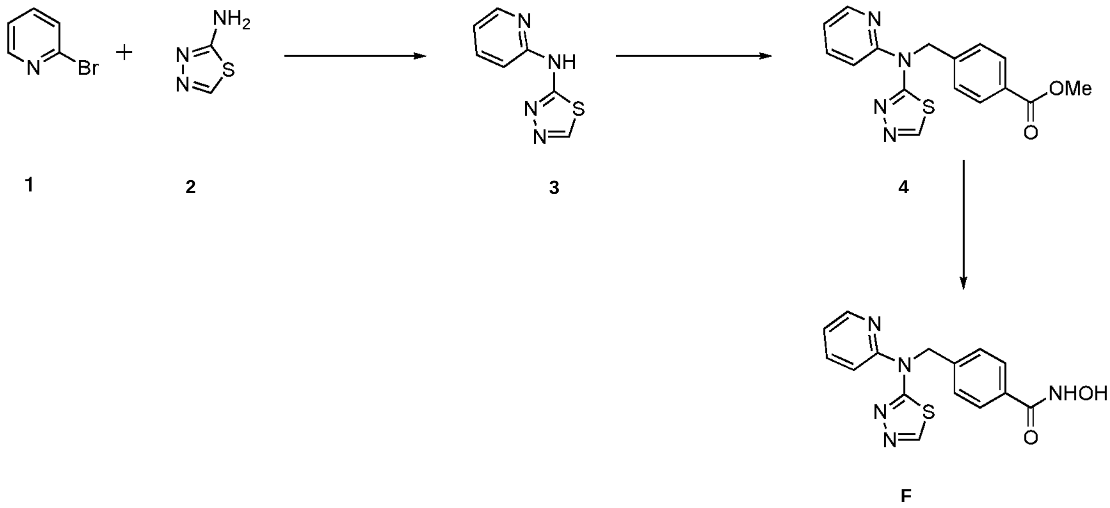
A fresh solution of NH_2OH in MeOH was prepared: [KOH (3.83g, 68.3mmol) in MeOH (20ml_) was added to NH_2OH.HCl (4.74g, 68.3mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to 4-(((1-methyl-1H-pyrazol-3-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** (440mg, 1.3mmol) followed by KOH (766mg, 13.0mmol) solubilized in MeOH (10mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30mL/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-(((1-methyl-1 H-pyrazol-3-yl)(pyridin-2-yl)amino)methyl)benzamide, **Example E,** as a light brown liquid (50mg, 11%).

^1H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 8.09 (ddd, J=5.0, 1.9, 0.8 Hz, 1H), 7.64 (d, J=8.3 Hz, 2H), 7.52 (d, J=2.3 Hz, 1H), 7.49 (ddd, J=8.7, 7.0, 1.9 Hz, 1H), 7.40 (d, J=8.4 Hz, 2H), 6.91 (d, J=8.6 Hz, 1H), 6.73 (ddd, J=7.1 , 5.1, 0.7 Hz, 1H), 6.10 (d, J=2.4 Hz, 1H), 5.26 (s, 2H), 3.81 (s, 3H).

LCMS (ES): Found 324.4 $[M+H]^+$.

Example F

N-Hydroxy-4-((pyridin-2-yl(1,3,4-thiadiazol-2-yl)amino)methyl)benzamide



2-Bromopyridine **(1)** (1.0g, 6.3mmol), 1,3,4-thiadiazol-2-amine **(2)** (0.64g, 6.3mmol), Xantphos (0.37g, 0.63mmol), and Cs_2C0_3 (3.1g, 9.4mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.29g, 0.31 mmol) was then added and the resulting reaction mixture was then heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(pyridin-2-yl)-1, 3, 4-thiadiazol-2-amine **(3)** as a yellow solid (0.33g, 30%).

LCMS (ES): Found 179.0 $[M+H]^+$.

NaH (60%) (53mg, 1.3mmol) was added portion-wise to N-(pyridin-2-yl)-1 ,3,4-thiadiazol-2-amine **(3)** (225mg,1 .26mmol) in DMF (8ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl)benzoate (336mg, 1.6mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((pyridin-2-yl(1,3,4-thiadiazol-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (1 18mg, 33%).

LCMS (ES): Found 327.3 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.01g, 18.1mmol) in MeOH (20ml_) was added to $NH_2OH.HCl$ (1.26g, 18.1mmol) in MeOH (20ml_) at

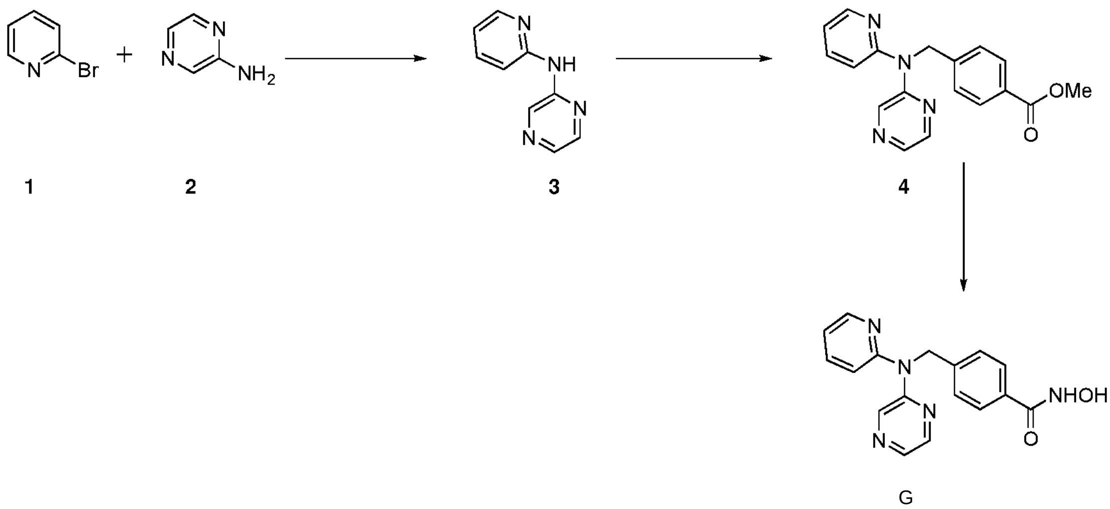
0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((pyridin-2-yl(1,3,4-thiadiazol-2-yl)amino)methyl)benzoate **(4)** (118mg, 0.36mmol) followed by KOH (203mg, 3.6mmol) solubilized in MeOH (10mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-((pyridin-2-yl(1,3,4-thiadiazol-2-yl)amino)methyl)benzamide, **Example F,** as a light brown liquid (15mg, 13%).

^{1}H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 8.96 (s, 1H), 8.44 (dd, J=5.0, 1.1 Hz, 1H), 7.72-7.78 (m, 1H), 7.69 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.2 Hz, 2H), 7.06-7.1 1 (m, 2H), 5.79 (s, 2H).

LCMS (ES): Found 328.1 $[M+H]^+$.

Example G

N-Hydroxy-4-((pyrazin-2-yl(pyridin-2-yl)amino)methyl)benzamide



2-Bromopyridine **(1)** (1.0g, 6.3mmol), pyrazin-2-amine **(2)** (0.67g, 6.9mmol), BINAP (0.12g, 0.18mmol), t-BuOK (0.99g, 8.8mmol) were combined in dry toluene (15 ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.1 1g,0.12mmol) was added, and the mixture heated at 90°C for 3 h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(pyridin-2-yl)pyrazin-2-amine **(3)** as a yellow solid (0.9g, 83%).

LCMS (ES): Found 173.1 $[M+H]^+$.

NaH (60%) (61 mg, 1.52mmol) was added portion-wise to N-(pyridin-2-yl)pyrazin-2-amine **(3)** (250mg,1.45mmol) in DMF (10mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (432mg, 1.88mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((pyrazin-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (380mg, 81%).

LCMS (ES): Found 321 .3 $[M+H]^+$.

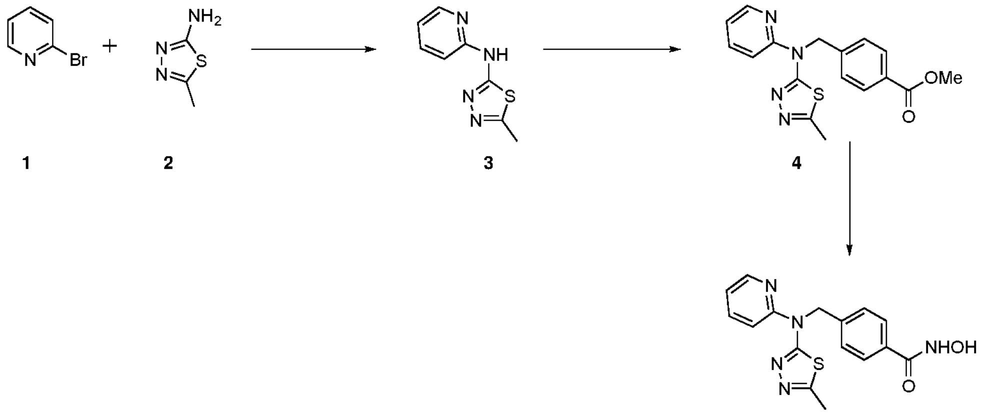
A fresh solution of NH_2OH in MeOH was prepared: [KOH (3.33g, 59.0mmol) in MeOH (20ml_) was added to NH_2OH.HCI (4.1g, 59.0mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((pyrazin-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** (380mg, 1.1mmol) followed by KOH (666mg, 11.8mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_2O (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-((pyrazin-2-yl(pyridin-2-yl)amino)methyl)benzamide, **Example G,** as a light cream solid (20mg, 5%).

^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.10 (br. s., 1H), 8.99 (br. s., 1H), 8.65 (d, J=1 .4 Hz, 1H), 8.32 (ddd, J=4.9, 1.9, 0.8 Hz, 1H), 8.27 (dd, J=2.7, 1.5 Hz, 1H), 8.10 (d, J=2.6 Hz, 1H), 7.74 (ddd, J=8.4, 7.3, 2.0 Hz, 1H), 7.64 (d, J=8.3 Hz, 2H), 7.36 (d, J=8.2 Hz, 2H), 7.33 (d, J=8.4 Hz, 1H), 7.06 (ddd, J=7.3, 4.9, 0.8 Hz, 1H), 5.45 (s, 2H).

LCMS (ES): Found 322.3 $[M+H]^+$.

Example H

N-Hydroxy-4-(((5-methyl-1,3,4-thiadiazol-2-yl)(pyridin-2-yl)amino)methyl)benzamide



2-Bromopyridine **(1)** (1.0g, 6.3mmol), 5-methyl-1,3,4-thiadiazol-2-amine **(2)** (0.947g, 8.2mmol), Xantphos (0.366g, 0.63mmol), and Cs_2C0_3 (3.09g, 9.4mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.289g, 0.31 mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide 5-methyl-N-(pyridin-2-yl)-1, 3, 4-thiadiazol-2-amine **(3)** as a yellow solid (0.22g, 18%).

LCMS (ES): Found 193.2 $[M+H]^+$.

NaH (60%) (109.3mg, 1.3mmol) was added portion-wise to 5-methyl-N-(pyridin-2-yl)-1 ,3,4-thiadiazol-2-amine **(3)** (500mg,2.6mmol) in DMF (8ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl)benzoate (775mg, 3.3mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:3) to furnish methyl 4-(((5-methyl-1,3,4-thiadiazol-2-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (134mg, 39%).

LCMS (ES): Found 341 .4 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.0g, 19.7mmol) in MeOH (20ml_) was added to $NH_2OH.HCl$ (1.36g, 19.7mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((5-methyl-1,3,4-thiadiazol-2-yl)(pyridin-2-

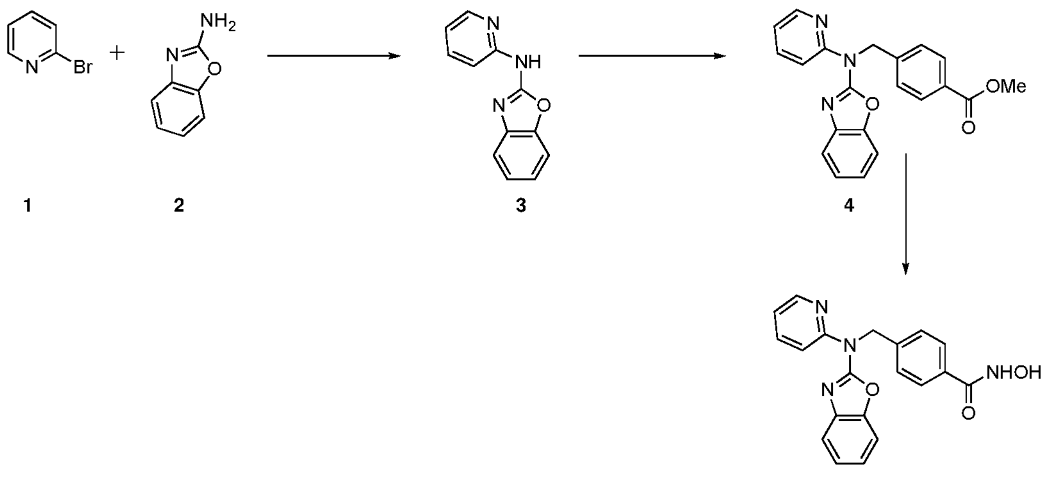
yl)amino)methyl)benzoate **(4)** (134mg, 0.39mmol) followed by KOH (221 mg, 3.9mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100mL). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-(((5-methyl-1,3,4-thiadiazol-2-yl)(pyridin-2-yl)amino)methyl)benzamide, **Example H,** as a light brown liquid (15mg, 11%).

^{1}H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 8.42 (dd, J=4.9, 1.1 Hz, 1H), 7.73 (ddd, J=8.6, 7.2, 1.8 Hz, 1H), 7.69 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.2 Hz, 2H), 7.02-7.09 (m, 2H), 5.72 (s, 2H), 2.65 (s, 3H).

LCMS (ES): Found 342.1 [M+H]$^+$.

Example I

4-((Benzo[d]oxazol-2-yl(pyridin-2-yl)amino)methyl)-N-hydroxybenzamide



2-Bromopyridine **(1)** (1.0g, 6.3mmol), benzo[d]oxazol-2-amine **(2)** (0.871 g, 6.4mmol), Xantphos (0.37g, 0.63mmol), and Cs_2C0_3 (3.09g, 9.4mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.289g, 0.31mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(pyridin-2-yl)benzo[d]oxazol-2-amine **(3)** as a yellow solid (0.8g, 60%).

LCMS (ES): Found 212.1 [M+H]$^+$.

NaH (60%) (53mg, 1.3mmol) was added portion-wise to N-(pyridin-2-yl)benzo[d]oxazol-2-amine **(3)** (265mg, 1.28mmol) in DMF (8mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (380mg, 1.66mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((benzo[d]oxazol-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (220mg, 48%).

LCMS (ES): Found 360.1 $[M+H]^+$.

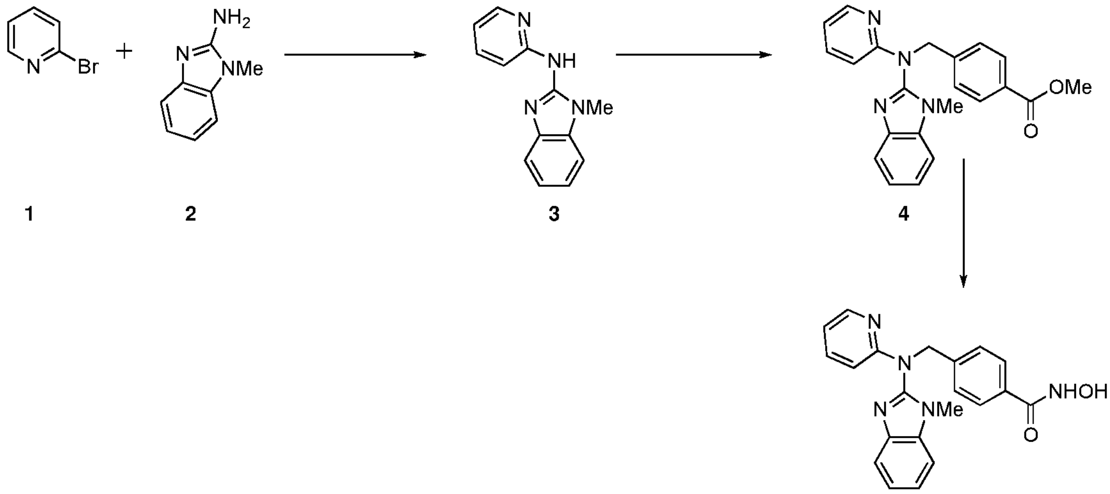
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.75g, 31.0mmol) in MeOH (15ml_) was added to NH_2OH.HCl (2.16g, 31.0mmol) in MeOH (15ml_) at 0°C. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((benzo[d]oxazol-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** (220mg, 0.62mmol) followed by KOH (348mg, 6.2mmol) solubilized in MeOH (5ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-((benzo[d]oxazol-2-yl(pyridin-2-yl)amino)methyl)-N-hydroxybenzamide, **Example I**, as a light orange solid (50mg, 23%).

^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.12 (br. s., 1H), 9.00 (br. s., 1H), 8.40 (dd, J=4.7, 1.8 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 7.88-7.94 (m, 1H), 7.65 (d, J=8.2 Hz, 2H), 7.47-7.55 (m, 2H), 7.41 (d, J=8.2 Hz, 2H), 7.26 (t, J=7.8 Hz, 1H), 7.14-7.22 (m, 2H), 5.59 (s, 2H).

LCMS (ES): Found 361.1 $[M+H]^+$.

Example J

N-Hydroxy-4-(((1-methyl-1H-benzo[d]imidazol-2-yl)(pyridin-2-yl)amino)methyl)benzamide



J

2-Bromopyridine **(1)** (1.0g, 6.3mmol), 1-methyl-1 H-pyrazol-3-amine **(2)** (1.21g, 6.9mmol), Xantphos (0.37g, 0.63mmol), and Cs_2C0_3 (4.1g, 12.6mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.29g, 0.31 mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide 1-methyl-N-(pyridin-2-yl)-1 H-benzo[d]imidazol-2-amine **(3)** as a yellow solid (0.35g, 25%).

LCMS (ES): Found 225.1 $[M+H]^+$.

NaH (60%) (32.8mg, 0.82mmol) was added portion-wise to 1-methyl-N-(pyridin-2-yl)-1 H-benzo[d]imidazol-2-amine **(3)** (175mg, 0.78mmol) in DMF (5mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (232mg, 1.01 mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((1-methyl-1H-benzo[d]imidazol-2-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (42mg, 16%).

LCMS (ES): Found 373.2 $[M+H]^+$.

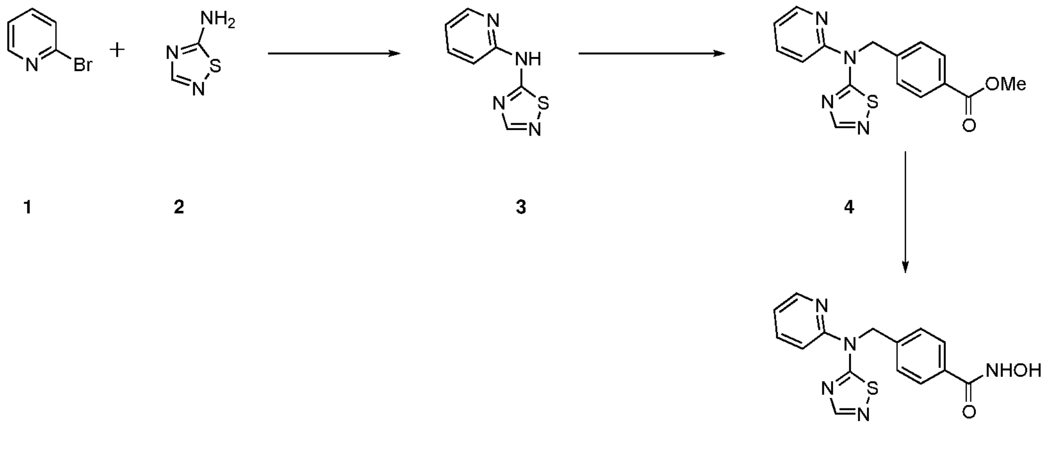
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.07g, 19.0mmol) in MeOH (10ml_) was added to NH_2OH.HCl (530mg, 19.0mmol) in MeOH (10ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((1-methyl-1H-benzo[d]imidazol-2-yl)(pyridin-2-yl)amino)methyl)benzoate **(4)** (142mg, 0.38mmol) followed by KOH (214mg, 3.8mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (10:90) to provide N-hydroxy-4-(((1-methyl-1 H-benzo[d]imidazol-2-yl)(pyridin-2-yl)amino)methyl)benzamide, **Example J,** as an off white solid (9mg, 7%).

^{1}H NMR (400 MHz, Methanol-^), δ_H ppm: 8.23 (dd, J=5.0, 1.1 Hz, 1H), 7.65 (d, J=8.3 Hz, 2H), 7.58-7.63 (m, 2H), 7.52 (d, J=8.2 Hz, 2H), 7.41 (dd, J=6.8, 1.9 Hz, 1H), 7.24-7.32 (m, 2H), 6.92 (dd, J=6.8, 5.1 Hz, 1H), 6.56 (d, J=8.4 Hz, 1H), 5.37 (s, 2H), 3.37-3.42 (m, 3H).

LCMS (ES): Found 374.3 $[M+H]^+$.

Example K

N-Hydroxy-4-((pyridin-2-yl(1,2,4-thiadiazol-5-yl)amino)methyl)benzamide



K

2-Bromopyridine **(1)** (1.0g, 6.3mmol), 1, 2, 4-thiadiazol-5-amine **(2)** (0.830g, 8.22mmol), Xantphos (0.366g, 0.63mmol), and Cs_2C0_3 (3.09g, 9.4mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.29g, 0.31 mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(pyridin-2-yl)-1 , 2, 4-thiadiazol-5-amine **(3)** as a yellow solid (0.1 88g, 16%).

LCMS (ES): Found 179.0 $[M+H]^+$

NaH (60%) (49mg, 1.23mmol) was added portion-wise to N-(pyridin-2-yl)-1 ,2,4-thiadiazol-5-amine **(3)** (210mg, 1.19mmol) in DMF (8ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl)benzoate (351 mg, 1.5mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((pyridin-2-yl(1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** as a light yellow solid (1 10mg, 28%).

LCMS (ES): Found 327.4 $[M+H]^+$.

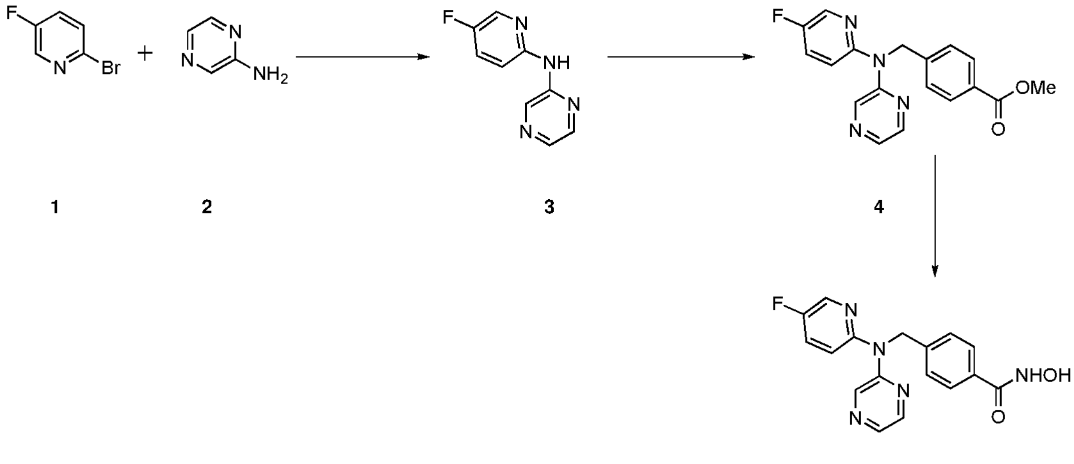
A fresh solution of NH_2OH in MeOH was prepared: [KOH (949mg, 16.9mmol) in MeOH (10ml_) was added to NH_2OH.HCI (1.17g, 16.9mmol) in MeOH (10ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((pyridin-2-yl(1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** (1 10mg, 0.33mmol) followed by KOH (185mg, 3.3mmol) solubilized in MeOH (5ml_). The reaction mixture was stirred at rt for 2 1h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-((pyridin-2-yl(1,2,4-thiadiazol-5-yl)amino)methyl)benzamide, **Example K,** as a light orange solid (1 1mg, 10%).

^{1}H NMR (400 MHz, Methanol-^), δ_H ppm: 8.54 (d, J=4.3 Hz, 1H), 8.22-8.31 (m, 1H), 7.81 (br. s., 1H), 7.65-7.76 (m, 2H), 7.08-7.38 (m, 4H), 5.82 (s, 2H).

LCMS (ES): Found 328.0 $[M+H]^+$.

Example L

4-(((5-Fluoropyridin-2-yl)(pyrazin-2-yl)amino)methyl)-N-hydroxybenzamide



1 2 3 4

L

2-Bromo-5-fluoropyridine **(1)** (1.0g, 5.71 mmol), pyrazin-2-amine **(2)** (543mg, 5.71 mmol), Xantphos (0.330g, 0.57mmol), Cs_2CO_3 (2.79g, 8.56mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g), and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.26g, 0.28mmol) was added and the reaction mixture was then heated at 90°C for 30h. It was then poured onto demineralized water (200 ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(5-fluoropyridin-2-yl)pyrazin-2-amine **(3)** as a yellow solid (0.56g, 51%).

LCMS (ES): Found 191.1 $[M+H]^+$.

NaH (60%) (39mg, 0.99mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)pyrazin-2-amine **(3)** (180mg, 0.94mmol) in DMF (5mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (281 mg, 1.23mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated in vacuo. The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((5-fluoropyridin-2-yl)(pyrazin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (190mg, 59%).

LCMS (ES): Found 339.1 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.57g, 28.1 mmol) in MeOH (15ml_) was added to $NH_2OH.HCl$ (1.95g, 28.1mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts;

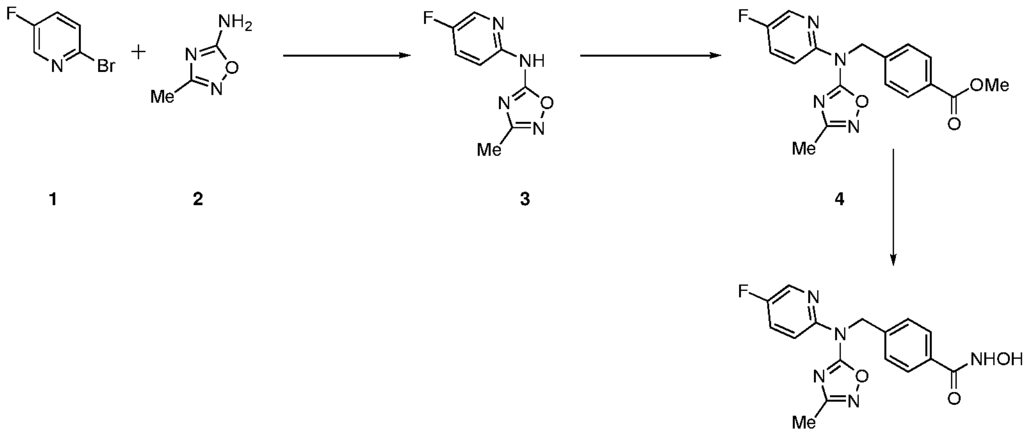
it was then added to methyl 4-(((5-fluoropyridin-2-yl)(pyrazin-2-yl)amino)methyl)benzoate **(4)** (190mg, 0.56mmol) followed by KOH (315mg, 5.6mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(pyrazin-2-yl)amino)methyl)-N-hydroxybenzamide, **Example L**, as a creamish solid (40mg, 21%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.08 (br. s, 1H), 8.84-9.09 (m, 1H), 8.54 (d, J=1 .4 Hz, 1H), 8.34 (d, J=3.1 Hz, 1H), 8.24 (dd, J=2.7, 1.5 Hz, 1H), 8.09 (d, J=2.7 Hz, 1H), 7.72 (ddd, J=9.0, 8.2, 3.1 Hz, 1H), 7.64 (d, J=8.3 Hz, 2H), 7.46 (dd, J=9.1 , 3.7 Hz, 1H), 7.37 (d, J=8.3 Hz, 2H), 5.42 (s, 2H)

LCMS (ES): Found 340.1 $[M+H]^+$.

Example M

4-(((5-Fluoropyridin-2-yl)(3-methyl-1 ,2,4-oxadiazol-5-yl)amino)methyl)-N-hydroxybenzamide



M

2-Bromo-5-fluoropyridine **(1)** (1.0g, 5.71mmol), 3-methyl-1, 2, 4-oxadiazol-5-amine **(2)** (566mg, 5.71 mmol), Xantphos (0.330g, 0.57mmol), and Cs_2C0_3 (2.79g, 8.56mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.261g, 0.28mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash

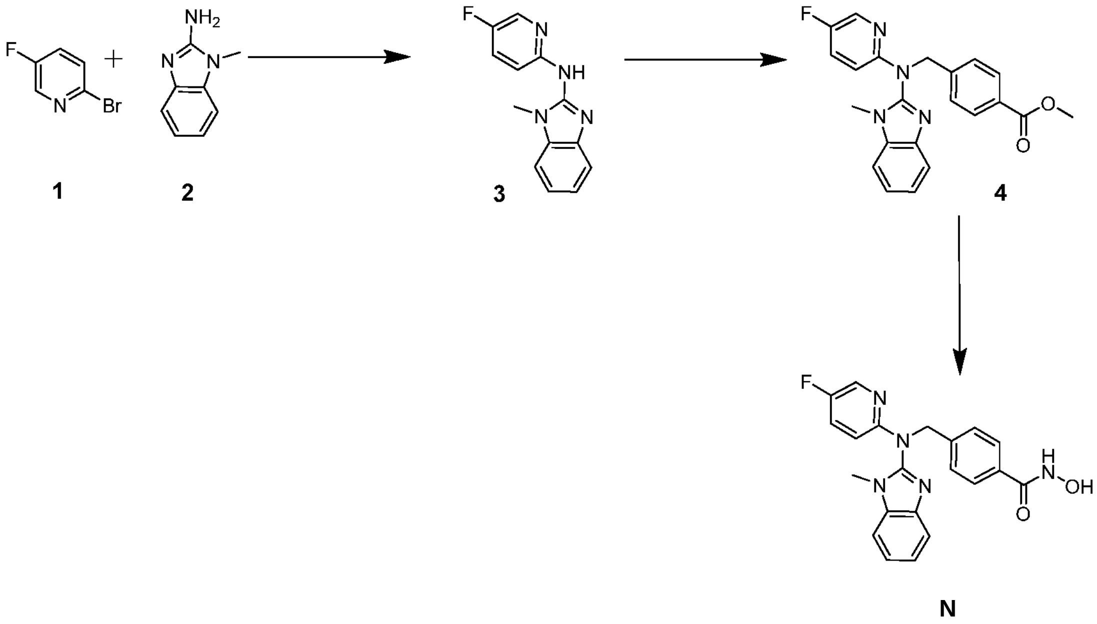
chromatography with EtOAc/Hexane (1:1) to provide N-(5-fluoropyridin-2-yl)-3-methyl-1, 2, 4-oxadiazol-5-amine **(3)** as a yellow solid (0.70g, 63%).
LCMS (ES): Found 195.0 $[M+H]^+$.

NaH (60%) (56mg, 1.4mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)-3-methyl-1,2,4-oxadiazol-5-amine **(3)** (260mg, 1.34mmol) in DMF (10ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (398mg, 1.7mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl-4-(((5-fluoropyridin-2-yl)(3-methyl-1 ,2,4-oxadiazol-5-yl)amino)methyl)benzoate **(4)** as a light yellow solid (170mg, 37%).
LCMS (ES): Found 343.1 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.39g, 24.8mmol) in MeOH (15ml_) was added to NH_2OH.HCl (1.72g, 24.8mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((5-fluoropyridin-2-yl)(3-methyl-1,2,4-oxadiazol-5-yl)amino)methyl)benzoate **(4)** (170mg, 0.49mmol) followed by KOH (278mg, 4.9mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(3-methyl-1 ,2,4-oxadiazol-5-yl)amino)methyl)-N-hydroxybenzamide, **Example M,** as a light orange solid (20mg, 12%).
^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.11 (br. s., 1H), 9.01 (br. s., 1H), 8.43 (d, J=3.0 Hz, 1H), 8.11 (dd, J=9.2, 3.8 Hz, 1H), 7.89 (td, J=8.6, 3.1 Hz, 1H), 7.67 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.2 Hz, 2H), 5.43 (s, 2H), 2.22 (s, 4H).
LCMS (ES): Found 344.1 $[M+H]^+$.

Example N

4-(((5-Fluoropyridin-2-yl)(1-methyl-1H-benzo[d]imidazol-2-yl)amino)methyl)-N-hydroxybenzamide



2-Bromo-5-fluoropyridine **(1)** (1.0g, 5.71mmol), 1-methyl-1H-benzo[d]imidazol-2-amine **(2)** (840mg, 5.71 mmol), Xantphos (0.33g, 0.57mmol), and Cs_2C0_3 (2.79g, 8.56mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.26g, 0.28mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(5-fluoropyridin-2-yl)-1-methyl-1H-benzo[d]imidazol-2-amine **(3)** as a yellow solid (0.56g, 41%).
LCMS (ES): Found 243.1 $[M+H]^+$.

NaH (60%) (27mg, 0.66mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)-1-methyl-1H-benzo[d]imidazol-2-amine **(3)** (154mg, 0.63mmol) in DMF (5mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (189mg, 0.82mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((5-fluoropyridin-2-yl)(1-methyl-1H-benzo[d]imidazol-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (165mg, 66%).

LCMS (ES): Found 391.2 [M+H]+.

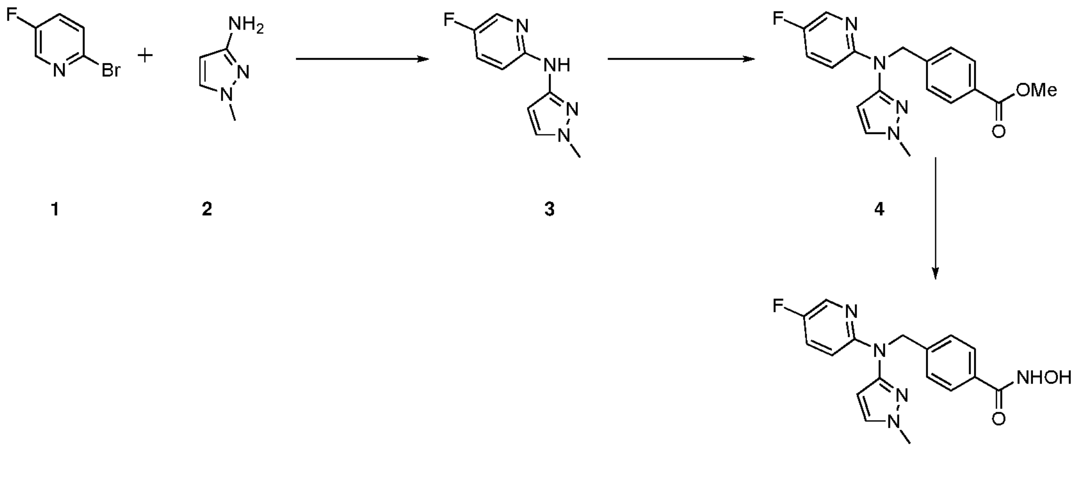
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.20g, 21.4mmol) in MeOH (15ml_) was added to NH_2OH.HCl (1.48g, 21.4mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((5-fluoropyridin-2-yl)(1-methyl-1 H-benzo[d]imidazol-2-yl)amino)methyl)benzoate **(4)** (165mg, 0.40mmol) followed by KOH (240mg, 4.0mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(1-methyl-1 H-benzo[d]imidazol-2-yl)amino)methyl)-N-hydroxybenzamide, **Example N,** as a light orange solid (20mg, 12%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 8.19 (d, J=2.9 Hz, 1H), 7.66 (d, J=8.2 Hz, 1H), 7.55-7.63 (m, 3H), 7.42-7.54 (m, 3H), 7.15-7.27 (m, 2H), 6.74 (dd, J=9.2, 3.4 Hz, 1H), 5.22-5.31 (m, 2H), 3.42 (s, 3H).

LCMS (ES): Found 392.25 [M+H]+.

Example O

4-(((5-Fluoropyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)-N-hydroxybenzamide



1 2 3 4

O

2-Bromo-5-fluoropyridine **(1)** (1.0g, 5.71mmol), 1-methyl-1 H-pyrazol-3-amine **(2)** (554mg, 5.71 mmol), Xantphos (0.330g, 0.57mmol), and Cs_2C0_3 (2.79g, 8.56mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.261 g, 0.28mmol) was then

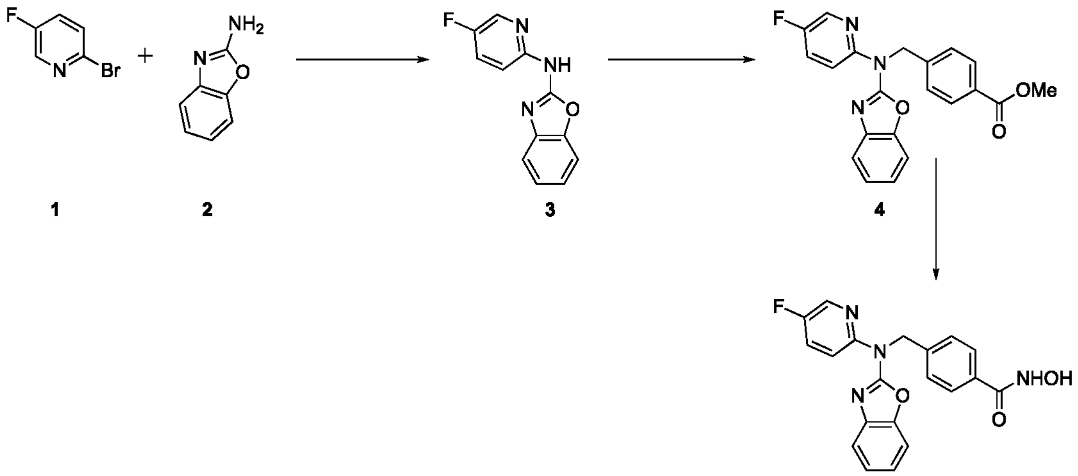
added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide 5-fluoro-N-(1 -methyl- 1H-pyrazol-3-yl)pyridin-2-amine **(3)** as a yellow solid (0.65g, 61%).
LCMS (ES): Found 193.0 $[M+H]^+$.

NaH (60%) (50mg, 1.25mmol) was added portion-wise to 5-fluoro-N-(1-methyl-1 H-pyrazol-3-yl)pyridin-2-amine **(3)** (230mg, 1.19mmol) in DMF (10ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (356mg, 1.55mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((5-fluoropyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)benzoate **(4)** as a light yellow solid (312mg, 76%).
LCMS (ES): Found 341.1 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (2.57g, 45.8mmol) in MeOH (15ml_) was added to NH_2OH.HCl (3.18g, 45.8mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl methyl 4-(((5-fluoropyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)benzoate **(4)** (312mg, 0.91 mmol) followed by KOH (512mg, 9.1mmol) solubilized in MeOH (5ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(1-methyl-1H-pyrazol-3-yl)amino)methyl)-N-hydroxybenzamide, **Example O,** as a cream solid (65mg, 20%).
^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.11 (br. s, 1H), 8.96 (br. s, 1H), 8.10 (d, J=3.1 Hz, 1H), 7.59-7.66 (m, 3H), 7.51 (ddd, J=9.3, 8.2, 3.1 Hz, 1H), 7.31 (d, J=8.1 Hz, 2H), 7.19 (dd, J=9.4, 3.7 Hz, 1H), 6.13 (d, J=2.3 Hz, 1H), 5.21 (s, 2H), 3.76 (s, 3H).
LCMS (ES): Found 342.1 $[M+H]^+$.

Example P

4-((Benzo[d]oxazol-2-yl(5-fluoropyridin-2-yl)amino)methyl)-N-hydroxybenzamide



P

2-Bromo-5-fluoropyridine **(1)** (1.0g, 5.71 mmol), benzo[d]oxazol-2-amine **(2)** (766mg, 5.71 mmol), Xantphos (0.33g, 0.57mmol), and Cs_2C0_3 (2.79g, 8.56mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.261g, 0.28mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(5-fluoropyridin-2-yl)benzo[d]oxazol-2-amine **(3)** as a yellow solid (0.6g, 46%).

LCMS (ES): Found 230.1 $[M+H]^+$.

NaH (60%) (36mg, 0.91 mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)benzo[d]oxazol-2-amine **(3)** (200mg, 0.87mmol) in DMF (8ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (259mg, 1.13mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((benzo[d]oxazol-2-yl(5-fluoropyridin-2-yl)amino)methyl)benzoate **(4)** as a light yellow solid (144mg, 43%).

LCMS (ES): Found 378.1 $[M+H]^+$.

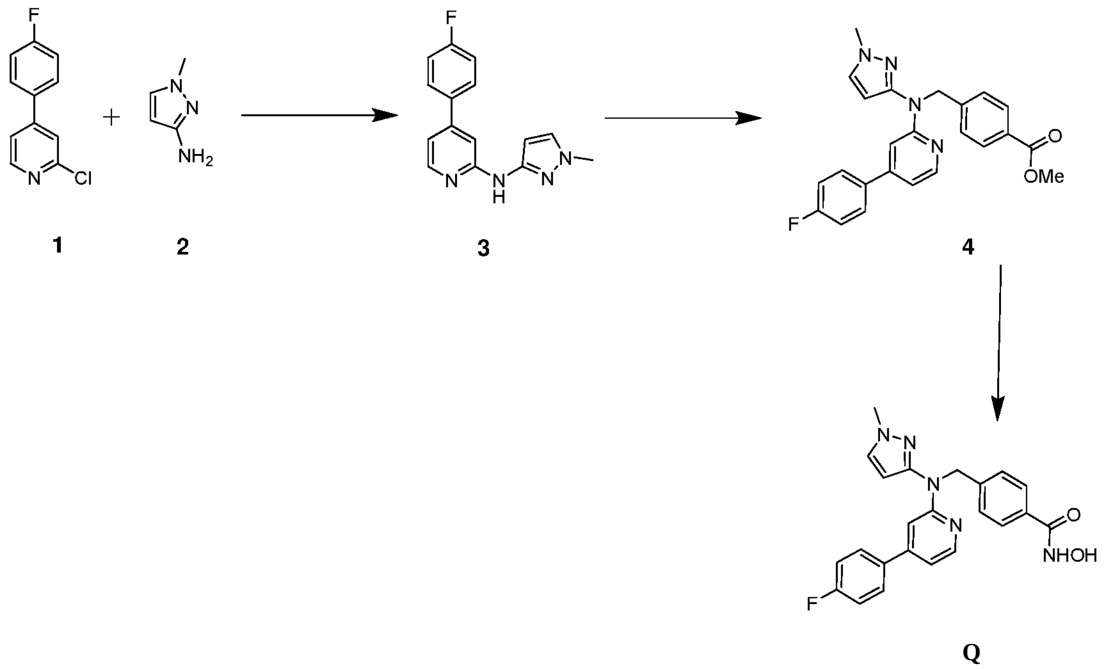
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.07g, 19.0mmol) in MeOH (15ml_) was added to NH_2OH.HCl (1.33g, 19.0mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((benzo[d]oxazol-2-yl(5-fluoropyridin-2-yl)amino)methyl)benzoate **(4)** (144mg, 0.38mmol) followed by KOH (214mg, 3.8mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-((benzo[d]oxazol-2-yl(5-fluoropyridin-2-yl)amino)methyl)-N-hydroxybenzamide, **Example P,** as an orange solid (30mg, 20%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.13 (br. s, 1H), 9.01 (br. s., 1H), 8.41 (d, J=3.1 Hz, 1H), 8.25 (dd, J=9.2, 3.8 Hz, 1H), 7.89 (ddd, J=9.2, 8.1, 3.1 Hz, 1H), 7.66 (d, J=8.3 Hz, 2H), 7.47-7.54 (m, 2H), 7.41 (d, J=8.2 Hz, 2H), 7.26 (td, J=7.7, 1.1 Hz, 1H), 7.13-7.20 (m, 1H), 5.54 (s, 2H).

LCMS (ES): Found 379.1 $[M+H]^+$.

Example Q

4-(((4-(4-Fluorophenyl)pyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)-N-hydroxybenzamide



2-Chloro-4-(4-fluorophenyl)pyridine **(1)** (1.0g, 4.8mmol), 1-methyl- 1H-pyrazol-3-amine **(2)** (470mg, 4.8mmol), Xantphos (0.28g, 0.48mmol), and Cs_2C0_3 (2.35g, 7.24mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.22g, 0.24mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide 4-(4-fluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)pyridin-2-amine **(3)** as a yellow solid (1.0g, 71%).
LCMS (ES): Found 269.1 $[M+H]^+$.

NaH (60%) (37mg, 0.93mmol) was added portion-wise to 4-(4-fluorophenyl)-N-(1-methyl-1H-pyrazol-3-yl)pyridin-2-amine **(3)** (250mg, 0.93mmol) in DMF (10mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (277mg, 1.2mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(1-methyl-1H-pyrazol-3-yl)amino)methyl)benzoate **(4)** as a light yellow solid (267mg, 68%).
LCMS (ES): Found 417.4 $[M+H]^+$.

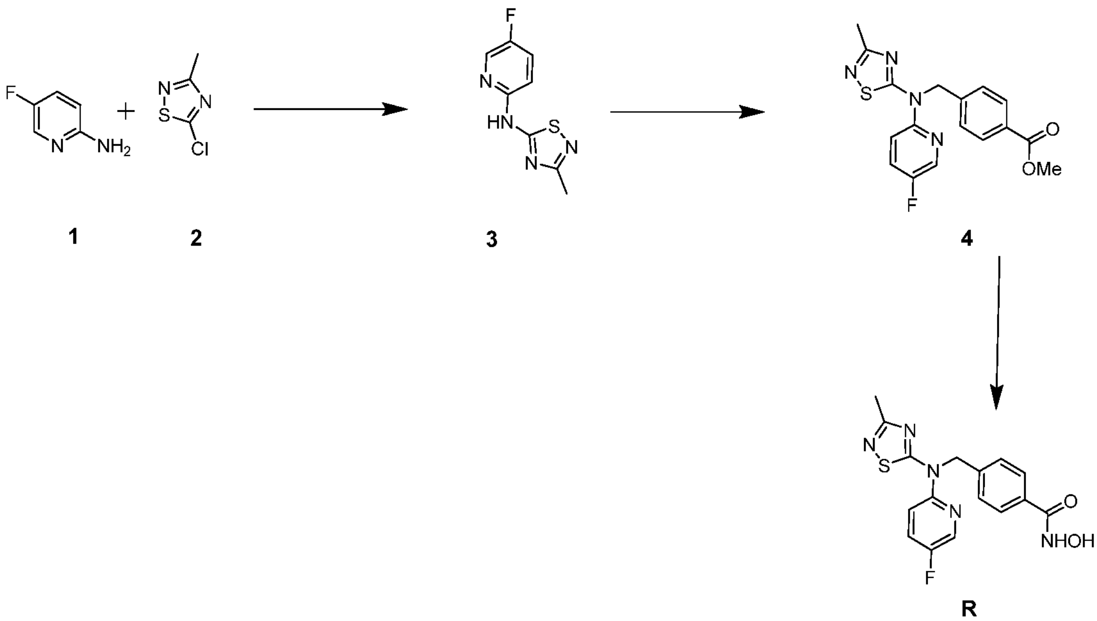
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.79g, 32.0mmol) in MeOH (15ml_) was added to NH_2OH.HCl (2.23g, 32.0mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)benzoate **(4)** (267mg, 0.64mmol) followed by KOH (359mg, 6.41 mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30mL/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to 4-(((4-(4-fluorophenyl)pyridin-2-yl)(1-methyl-1 H-pyrazol-3-yl)amino)methyl)-N-hydroxybenzamide, **Example Q,** as an off white solid (30mg, 11%).

[1]H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.11 (br. s, 1H), 9.00 (br. s, 1H), 8.19 (d, J=5.3 Hz, 1H), 7.59-7.71 (m, 5H), 7.24-7.39 (m, 5H), 6.98-7.05 (m, 1H), 6.26 (d, J=2.2 Hz, 1H), 5.30 (s, 2H), 3.74-3.79 (m, 3H).

LCMS (ES): Found 418.2 $[M+H]^+$.

Example R

4-(((5-Fluoropyridin-2-yl)(3-methyl-1 ,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide



5-Fluoropyridin-2-amine **(1)** (1.0g, 8.9mmol), 5-chloro-3-methyl-1, 2, 4-thiadiazole **(2)** (1.19g, 8.9mmol), Xantphos (0.52g, 0.89mmol), and Cs_2CO_3 (4.35g, 13.3mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.41 g, 0.44mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. The reaction mixture was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to provide N-(5-fluoropyridin-2-yl)-3-methyl-1, 2, 4-thiadiazol-5-amine **(3)** as a yellow solid (1.2g, 67%).

LCMS (ES): Found 211.1 $[M+H]^+$.

NaH (60%) (59mg, 1.49mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)-3-methyl-1,2,4-thiadiazol-5-amine **(3)** (300mg,1 .42mmol) in DMF (7ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (425mg, 1.85mmol) was added, and stirring was continued at 70°C under

Ar(g) for 1h in the dark. The reaction mixture was then poured onto water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl-4-(((5-fluoropyridin-2-yl)(3-methyl-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** as a yellow solid (480mg, 90%).

LCMS (ES): Found 359.3 $[M+H]^+$.

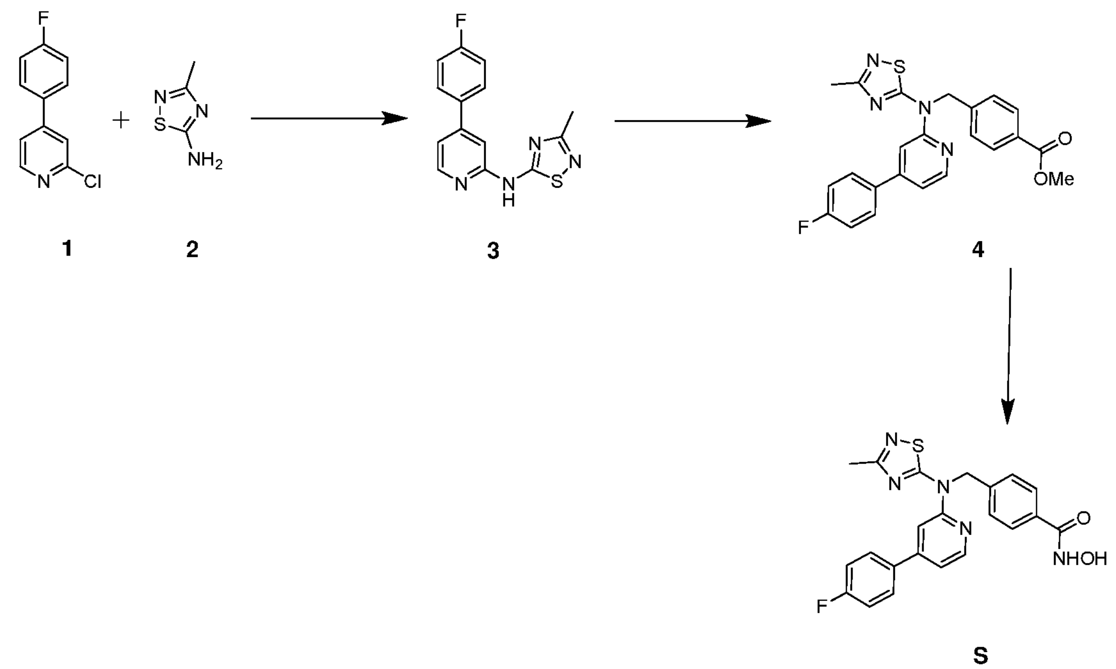
A fresh solution of NH_2OH in MeOH was prepared: [KOH (4.63g, 67.0mmol) in MeOH (20ml_) was added to $NH_2OH.HCl$ (3.76g, 67.0mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((5-fluoropyridin-2-yl)(3-methyl-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** (480mg, 1.3mmol) followed by KOH (750mg, 1.3mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100mL). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(3-methyl-1 ,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide, **Example R,** as an orange solid (90mg, 19%).

^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.16 (br. s., 1H), 9.03 (br. s., 1H), 8.60 (d, J=2.9 Hz, 1H), 7.86 (td, J=8.7, 2.8 Hz, 1H), 7.64-7.76 (m, 2H), 7.19-7.34 (m, 3H), 5.77 (s, 2H), 2.39 (s, 3H).

LCMS (ES): Found 359.8 $[M+H]^+$.

Example S

4-(((4-(4-Fluorophenyl)pyridin-2-yl)(3-methyl-1,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide



2-Chloro-4-(4-fluorophenyl)pyridine **(1)** (1.0g, 4.8mmol), 3-methyl-1, 2, 4-thiadiazol-5-amine **(2)** (0.56g, 4.8mmol), Xantphos (0.279g, 0.48mmol), and Cs_2C0_3 (2.35g, 7.24mmol) were combined in dry 1,4-dioxane (15mL). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.22g, 0.24mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(4-(4-fluorophenyl)pyridin-2-yl)-3-methyl-1 , 2, 4-thiadiazol-5-amine **(3)** as a yellow solid (1.1g, 80%).
LCMS (ES): Found 287.1 $[M+H]^+$.

NaH (60%) (42mg, 1.05mmol) was added portion-wise to N-(4-(4-fluorophenyl)pyridin-2-yl)-3-methyl-1 ,2,4-thiadiazol-5-amine **(3)** (300mg, 1.05mmol) in DMF (10ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl)benzoate (312mg, 1.36mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(3-methyl-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** as a yellow solid (325mg, 74%).
LCMS (ES): Found 421.1 $[M+H]^+$.

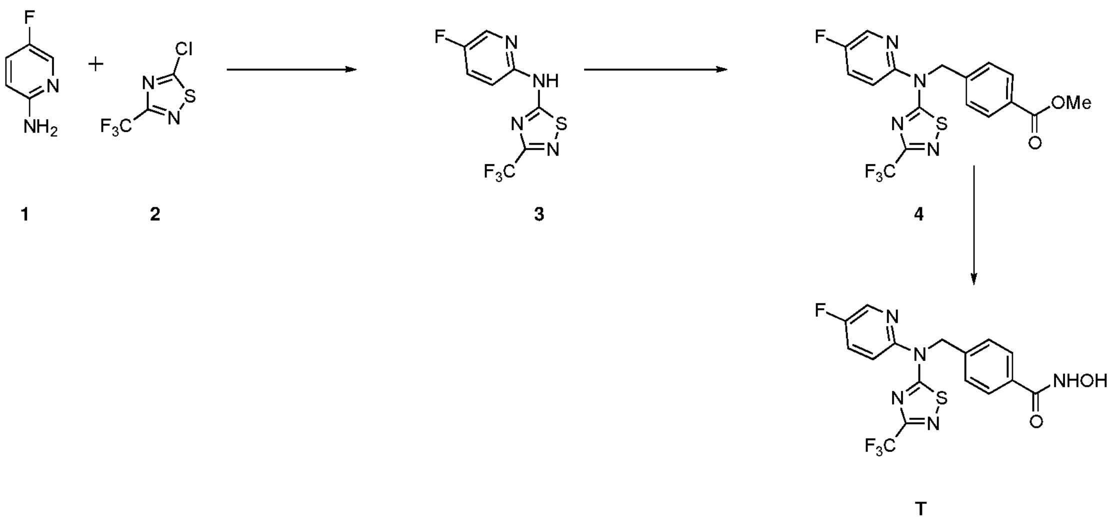
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.96g, 35mmol) in MeOH (10ml_) was added to NH_2OH.HCl (2.43g, 35mmol) in MeOH (10ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(3-methyl-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** (319mg, 0.69mmol) followed by KOH (392mg, 7.0mmol) solubilized in MeOH (10mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to 4-(((4-(4-fluorophenyl)pyridin-2-yl)(3-methyl-1 ,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide, **Example S,** as an off white solid (58mg, 19%).

^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.13 (br. s., 1H), 9.02 (br. s., 1H), 8.59 (d, J=5.3 Hz, 1H), 7.82 (dd, J=8.7, 5.3 Hz, 2H), 7.67 (d, J=8.2 Hz, 2H), 7.43-7.51 (m, 2H), 7.27-7.40 (m, 4H), 5.92 (s, 2H), 2.40 (s, 3H).

LCMS (ES): Found 436.4 $[M+H]^+$.

Example T

4-(((5-Fluoropyridin-2-yl)(3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide



5-Fluoropyridin-2-amine **(1)** (1.0g, 8.9mmol), 5-chloro-3-(trifluoromethyl)-1 , 2, 4-thiadiazole **(2)** (1.68g, 8.9mmol), Xantphos (0.52g, 0.89mmol), and Cs_2C0_3 (4.35g, 13.3mmol) were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.41g, 0.44mmol) was then added and the resulting reaction mixture was heated at 90°C

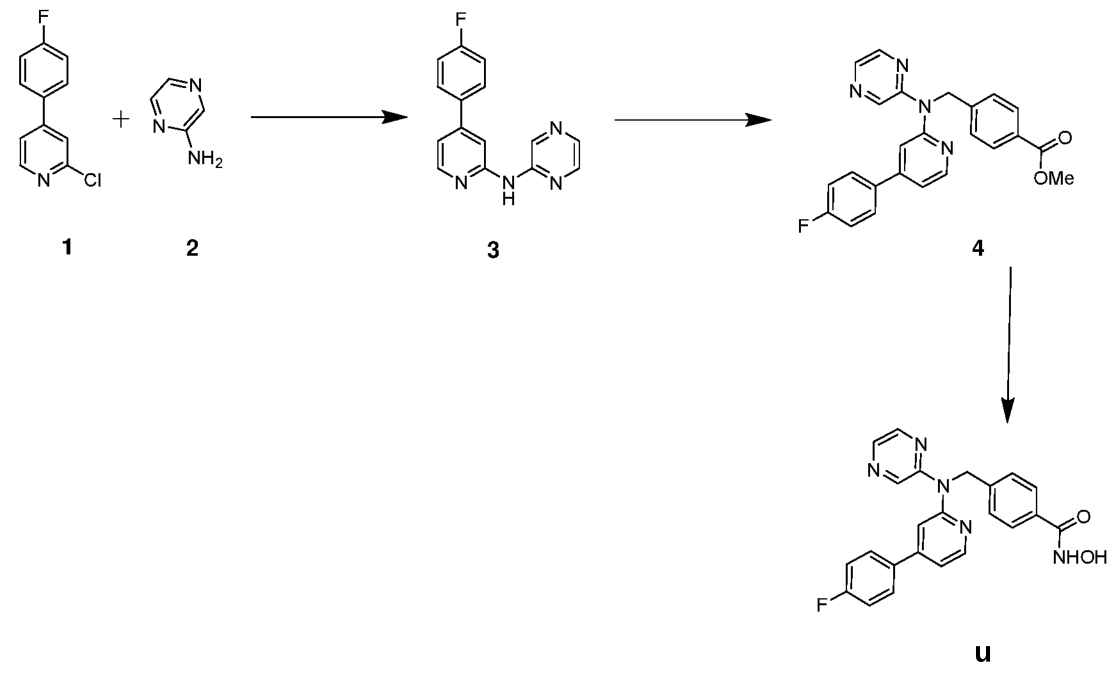
for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to provide N-(5-fluoropyridin-2-yl)-3-(trifluoromethyl)-l ,2,4-thiadiazol-5-amine **(3)** as a yellow solid (900mg, 38%).
LCMS (ES): Found 265.1 $[M+H]^+$.

NaH (60%) (61 mg, 1.51mmol) was added portion-wise to N-(5-fluoropyridin-2-yl)-3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-amine **(3)** (400mg,1.51mmol) in DMF (10ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (451 mg, 1.85mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((5-fluoropyridin-2-yl)(3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(3)** as a yellow solid (535mg, 82%).
LCMS (ES): Found 413.3 $[M+H]^+$.

A fresh solution of NH_2OH in MeOH was prepared: [KOH (3.63g, 64.0mmol) in MeOH (20ml_) was added to NH_2OH.HCI (4.47g, 64.0mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((5-fluoropyridin-2-yl)(3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(3)** (535mg, 1.2mmol) followed by KOH (720mg, 13.0mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2CI_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2CI_2 (1:9) to provide 4-(((5-fluoropyridin-2-yl)(3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-yl)amino)methyl)-N-hydroxybenzamide, **Example T,** as an orange solid (90mg, 17%).
^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.18 (br. s., 1H), 9.06 (br. s., 1H), 8.73 (d, J=2.7 Hz, 1H), 7.97 (td, J=8.6, 2.6 Hz, 1H), 7.69 (d, J=8.2 Hz, 2H), 7.46 (dd, J=9.0, 2.8 Hz, 1H), 7.31 (d, J=7.8 Hz, 2H), 5.80 (br. s., 2H), 5.72-5.87 (m, 1H).
LCMS (ES): Found 414.3 $[M+H]^+$.

Example U

4-(((4-(4-Fluorophenyl)pyridin-2-yl)(pyrazin-2-yl)amino)methyl)-N-hydroxybenzamide



NaH (60%) (47mg, 1.19mmol) was added portion-wise to N-(4-(4-fluorophenyl)pyridin-2-yl)pyrazin-2-amine **(3)** (prepared using conditions as per Examples above) (300mg,1 .13mmol) in DMF (10mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl)benzoate (337mg, 1.47mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(pyrazin-2-yl)amino)methyl)benzoate **(4)** as a yellow solid (220mg, 46%).

LCMS (ES): Found 414.4 $[M+H]^+$.

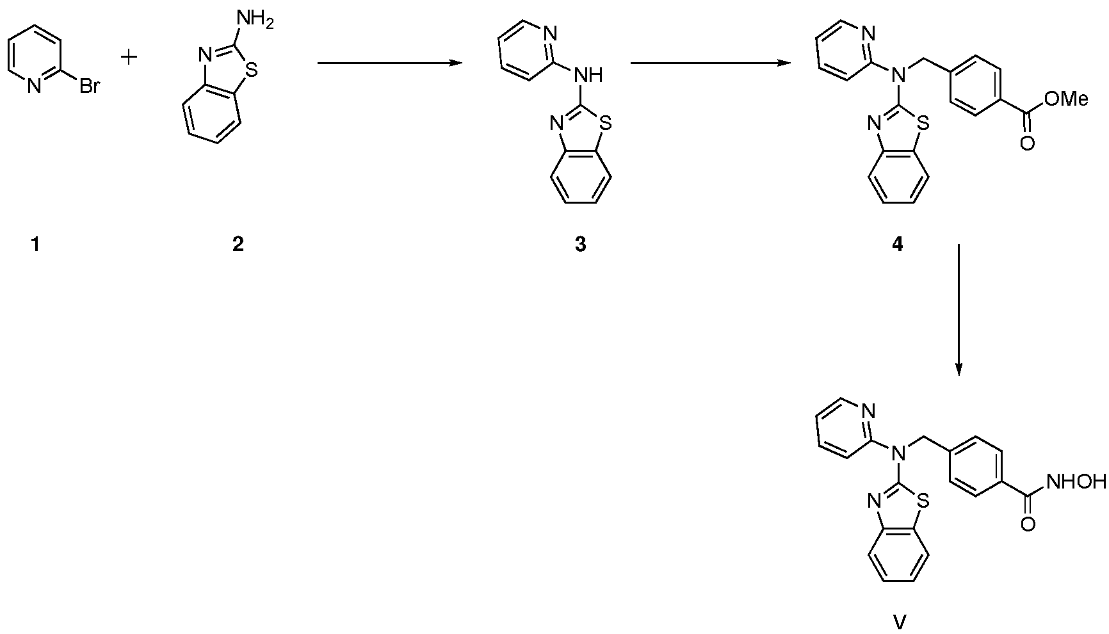
A fresh solution of NH_2OH in MeOH was prepared: [KOH (1.49g, 26.9mmol) in MeOH (10ml_) was added to NH_2OH.HCI (1.86g, 26.9mmol) in MeOH (10ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-(((4-(4-fluorophenyl)pyridin-2-yl)(pyrazin-2-yl)amino)methyl)benzoate **(4)** (220mg,0.53mmol) followed by KOH (298mg, 5.3mmol) solubilized in MeOH (10mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to 4-(((4-(4-fluorophenyl)pyridin-2-yl)(pyrazin-2-yl)amino)methyl)-N-hydroxybenzamide, **Example U,** as an off white solid (35mg, 16%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.10 (br. s., 1H), 8.99 (br. s., 1H), 8.69 (d, J=1.4 Hz, 1H), 8.36 (d, J=5.3 Hz, 1H), 8.28 (dd, J=2.7, 1.5 Hz, 1H), 8.11 (d, J=2.7 Hz, 1H), 7.76-7.86 (m, 2H), 7.64 (d, J=8.4 Hz, 2H), 7.42 (d, J=8.2 Hz, 2H), 7.38 (dd, J=5.3, 1.4 Hz, 1H), 7.34 (t, J=8.9 Hz, 2H), 5.53 (s, 2H).

LCMS (ES): Found 416.1 $[M+H]^+$.

Example V

4-((Benzo[d]thiazol-2-yl(pyridin-2-yl)amino)methyl)-N-hydroxybenzamide



NaH (60%) (75mg, 1.8mmol) was added portion-wise to N-(pyridin-2-yl)benzo[d]thiazol-2-amine **(3)** (prepared using conditions as per Examples above) (430mg, 1.8mmol) in DMF (10mL) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (563mg, 2.4mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2SO_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((benzo[d]thiazol-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** as a yellow solid (300mg, 42%).

LCMS (ES): Found 376.1 $[M+H]^+$.

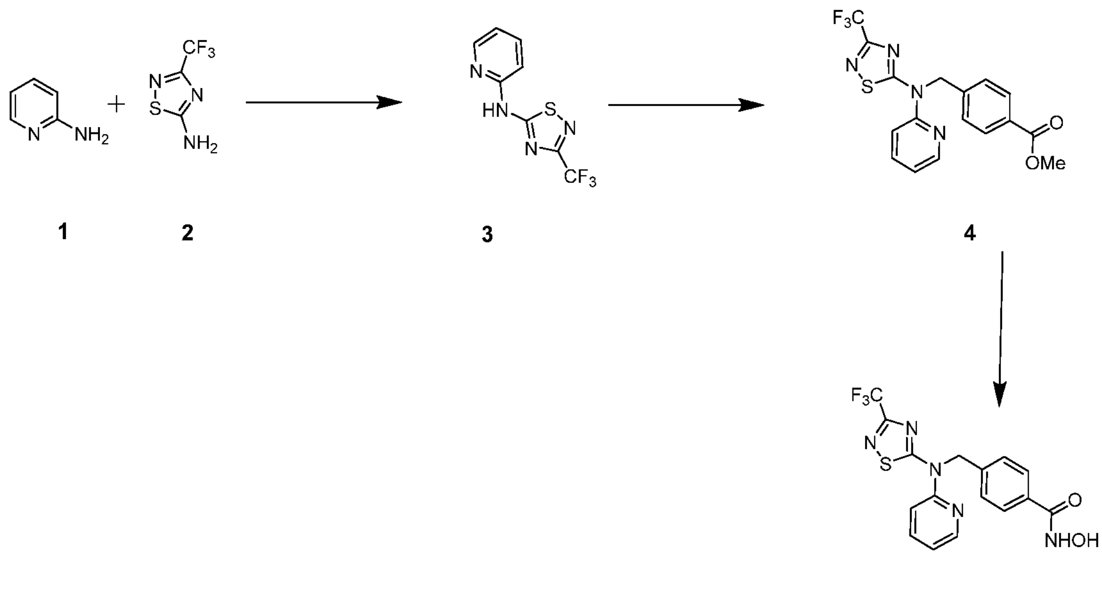
A fresh solution of NH_2OH in MeOH was prepared: [KOH (2.24g, 40.0mmol) in MeOH (15ml_) was added to NH_2OH.HCl (2.78g, 40.0mmol) in MeOH (15ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((benzo[d]thiazol-2-yl(pyridin-2-yl)amino)methyl)benzoate **(4)** (300mg, 0.8mmol) followed by KOH (449mg, 8.0mmol) solubilized in MeOH (5mL). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30ml_/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide 4-((benzo[d]thiazol-2-yl(pyridin-2-yl)amino)methyl)-N-hydroxybenzamide, **Example V,** as a light orange solid (60mg, 20%).

^{1}H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.15 (br. s, 1H), 8.99 (br. s, 1H), 8.50 (dd, J=4.8, 1.4 Hz, 1H), 7.93 (d, J=7.6 Hz, 1H), 7.78-7.86 (m, 1H), 7.68 (d, J=8.2 Hz, 2H), 7.64 (d, J=7.9 Hz, 1H), 7.33-7.39 (m, 1H), 7.21-7.31 (m, 3H), 7.11-7.20 (m, 2H), 5.82 (s, 2H).

LCMS (ES): Found 377.1 $[M+H]^+$.

Example W

N-Hydroxy-4-((pyridin-2-yl(3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl)amino)methyl)benzamide



1 2 3 4

W

Pyridin-2-amine **(1)** (1.0g, 10.6mmol), 5-chloro-3-(trifluoromethyl)-1,2,4-thiadiazole **(2)** (1.82g, 10.6mmol), Xantphos (0.61g, 1.06mmol), and Cs_2C0_3 (5.18g, 15.9mmol)

were combined in dry 1,4-dioxane (15ml_). The reaction mixture was degassed with N_2(g) and placed under vacuum for 10min. $Pd_2(dba)_3$ (0.49g, 0.53mmol) was then added and the resulting reaction mixture was heated at 90°C for 30h. It was then poured onto demineralized water (200ml_), and extracted with EtOAc (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (1:1) to provide N-(pyridin-2-yl)-3-(trifluoromethyl)-1,2,4-thiadiazol-5-amine **(3)** as a yellow solid (1.4g, 57%).
LCMS (ES): Found 247.2 $[M+H]^+$.

NaH (60%) (49mg, 1.21mmol) was added portion-wise to N-(pyridin-2-yl)-3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-amine **(3)** (300mg,1.21mmol) in DMF (10ml_) at 5°C under Ar(g). The reaction mixture was stirred for 20min, then methyl 4-(bromomethyl) benzoate (363mg, 1.58mmol) was added, and stirring was continued at 70°C under Ar(g) for 1h in the dark. The reaction mixture was then poured onto demineralized water (100ml_), and extracted with EtOAc (3 x 50ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with EtOAc/Hexane (3:7) to furnish methyl 4-((pyridin-2-yl(3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** as a yellow solid (450mg, 90%).
LCMS (ES): Found 395.3 $[M+H]^+$.

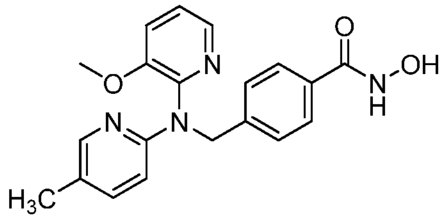
A fresh solution of NH_2OH in MeOH was prepared: [KOH (3.56g, 63.4mmol) in MeOH (20ml_) was added to NH_2OH.HCl (4.41g, 63.4mmol) in MeOH (20ml_) at 0°C]. The reaction mixture was stirred for 20min at 0°C, then filtered to remove salts; it was then added to methyl 4-((pyridin-2-yl(3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl)amino)methyl)benzoate **(4)** (500mg, 1.2mmol) followed by KOH (712mg, 12.6mmol) solubilized in MeOH (10ml_). The reaction mixture was stirred at rt for 21h, and then concentrated *in vacuo,* poured onto brine/H_20 (30mL/70mL), and extracted with CH_2Cl_2 (3 x 100ml_). The organic phases were combined, dried over Na_2S0_4, filtered and subsequently concentrated *in vacuo.* The resulting residue was purified by flash chromatography with MeOH/CH_2Cl_2 (1:9) to provide N-hydroxy-4-((pyridin-2-yl(3-(trifluoromethyl)-1 ,2,4-thiadiazol-5-yl)amino)methyl)benzamide, **Example W,** as an off white solid (20mg, 4%).
^1H NMR (400 MHz, DMSO-d_6), δ_H ppm: 11.15 (br. s., 1H), 9.03 (br. s., 1H), 8.63-8.68 (m, J=5.0, 0.9 Hz, 1H), 7.97 (ddd, J=8.7, 7.2, 1.8 Hz, 1H), 7.69 (d, J=8.4 Hz,

2H), 7.41 (d, J=8.6 Hz, 1H), 7.32 (d, J=8.3 Hz, 2H), 7.28 (dd, *J=7.0,* 5.3 Hz, 1H), 5.80 (s, 2H).

LCMS (ES): Found 396.3 $[M+H]^+$.

Example X

N-Hydroxy-4-(((3-methoxypyridin-2-yl)-(5-methylpyridin-2-yl)amino)methyl)benzamide

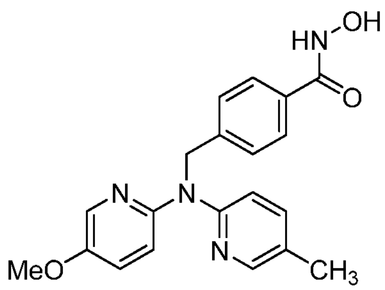


^{1}H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 7.97 (d, *J=4.*9 Hz, 1H), 7.89 (d, *J=2.3* Hz, 1H), 7.61 (d, *J*=7.8 Hz, 2H), 7.46 (t, *J*=7.5 Hz, 3H), 7.33 (dd, J^8.5, 2.4 Hz, 1H), 7.22 (dd, J^8.2, 4.8 Hz, 1H), 6.41 (d, *J*=8.5 Hz, 1H), 5.31 (s, 2H), 3.73 (s, 3H), 2.20 (s, 3H).

LCMS (ES): Found 365.0 $[M+H]^+$.

Example Y

N-Hydroxy-4-(((5-methoxypyridin-2-yl)(5-methylpyridin-2-yl)amino)methyl)benzamide

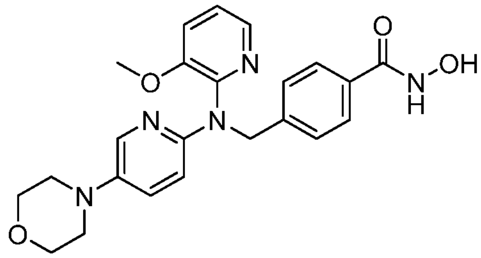


^{1}H NMR (400 MHz, Methanol-^), δ_H ppm: 7.99 (dd, **^=4.8,** 2.6 Hz, 2H), 7.62 (d, *J*=8.0 Hz, 2H), 7.41 (dd, J^8.2, 4.9 Hz, 3H), 7.31 (dd, ^=9.1, 3.1 Hz, 1H), 7.14 (d, *J*=8.9 Hz, 1H), 6.84 (d, *J*=8.5 Hz, 1H), 5.36 (s, 2H), 3.83 (s, 3H), 2.22 (s, 3H).

LCMS (ES): Found 365.0 $[M+H]^+$.

Example Z

N-Hydroxy-4-(((3-methoxypyridin-2-yl)(5-morpholinopyridin-2-yl)amino)methyl)benzamide

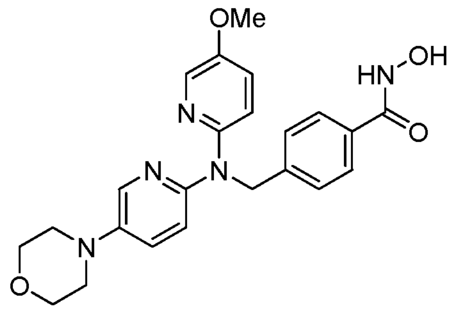


[1]H NMR (400 MHz, Methanol-^), δ_H ppm: 7.94 (dd, **^=4.8,** 1.5 Hz, 1H), 7.78 (d, *J*=3.0 Hz, 1H), 7.61 (d, *J*=8.3 Hz, 2H), 7.38-7.51 (m, 3H), 7.27 (dd, J^9.0, 3.1 Hz, 1H), 7.17 (dd, **^=8.1**, 4.8 Hz, 1H), 6.51 (d, *J*=9.0 Hz, 1H), 5.31 (s, 2H), 3.77-3.89 (m, 4H), 3.72 (s, 3H), 2.97-3.08 (m, 4H).

LCMS (ES): Found 436.0 $[M+H]^+$.

Example AA

N-Hydroxy-4-(((5-methoxypyridin-2-yl)(5-morpholinopyridin-2-yl)amino)methyl)benzamide

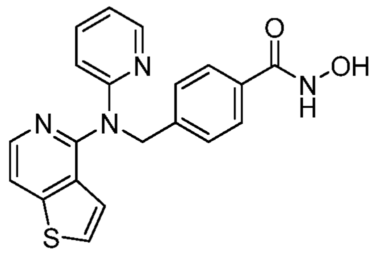


[1]H NMR (400 MHz, Methanol-^), δ_H ppm: 7.88-7.95 (m, 2H), 7.58-7.66 (m, 2H), 7.42 (d, *J*=8.0 Hz, 2H), 7.33 (dd, *J*=9.0, 3.1 Hz, 1H), 7.26 (dd, ^=9.1, 3.1 Hz, 1H), 6.99 (dd, J^9.0, 4.5 Hz, 2H), 5.34 (s, 2H), 3.71-3.94 (m, 7H), 3.04-3.15 (m, 4H).

LCMS (ES): Found 436.0 $[M+H]^+$.

Example BB

N-Hydroxy-4-((pyridin-2-yl(thieno[3,2-c]pyridin-4-yl)amino)methyl)benzamide

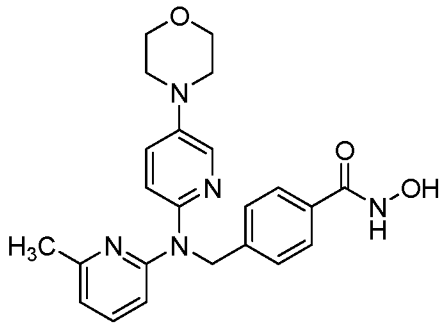


[1]H NMR (400 MHz, Methanol-cf_4), δ_H ppm: 7.97-8.10 (m, 1H), 7.76 (dd, *J* = 9.3, 7.1 Hz, 3H), 7.33-7.69 (m, 5H), 7.14 (d, *J*=5.4 Hz, 1H), 6.98 (d, J=9.1 Hz, 1H), 6.64 (t, *J*=6.8 Hz, 1H), 5.56 (s, 2H).

LCMS (ES): Found 377.0 $[M+H]^+$.

Example CC

N-Hydroxy-4-(((6-methylpyridin-2-yl)(5-morpholinopyridin-2-yl)amino)methyl)benzamide

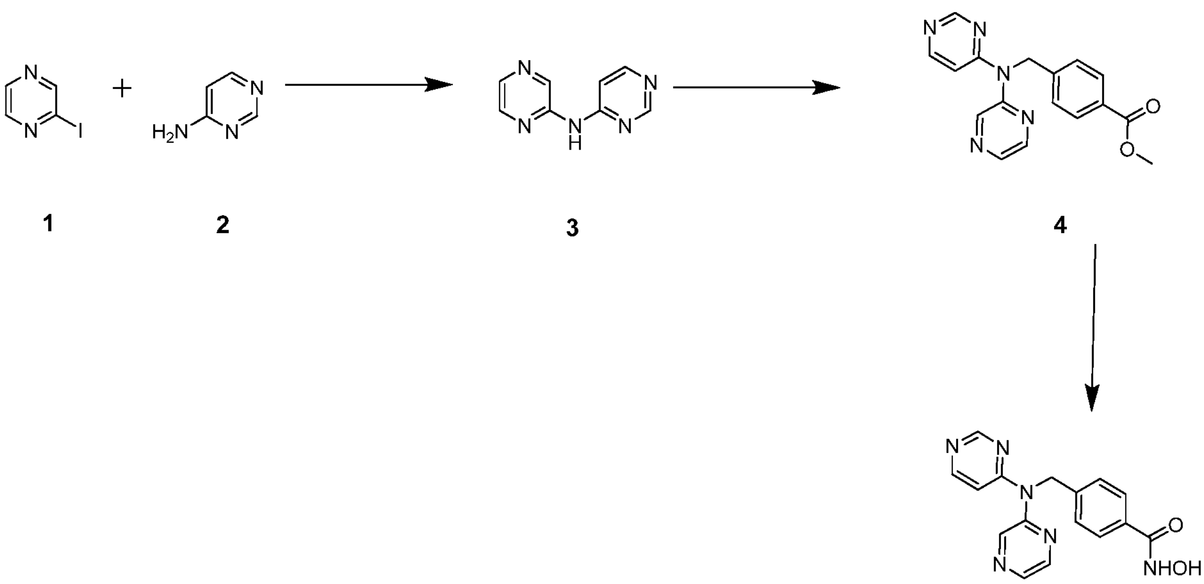


[1]H NMR (400 MHz, Methanol-cf$_4$), δ_H ppm: 7.99 (d, *J*=3.0 Hz, 1H), 7.62 (d, *J=7.8* Hz, 2H), 7.42 (d, *J*=8.1 Hz, 2H), 7.34-7.39 (m, 2H), 7.14 (d, *J*=8.9 Hz, 1H), 6.64 (dd, *J=8.*1, 7.8 Hz, 2H), 5.39 (s, 2H), 3.79-3.86 (m, 4H), 3.14 (dd, J^6.1, 3.6 Hz, 4H), 2.37 (s, 3H).

LCMS (ES): Found 420.0 [M+H]$^+$.

Example DD

N-Hydroxy-4-{[(pyrazin-2-yl)(pyrimidin-4-yl)amino]methyl}benzamide



DD

A solution of 2-iodopyrazine **(1)** (1.2g, 5.83mmol), pyrimidin-4-amine **(2)** (609mg, 6.41 mmol), Cs_2C0_3 (3.80g, 11.65mmol) and Xantphos (148mg, 0.26mmol) in 1,4-Dioxane (15ml_) was purged with N_2(g) for 10 min. $Pd_2(dba)_3$ (107mg, 0.12 mmol) was added and mixture was heated to 90°C for 3h. Reaction was cooled to rt and partitioned between water (300ml_) and EtOAc (3 x 100ml_). Combined organics were washed with water (50ml_), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/MeOH (1:0-9:1) to yield **(3)** (678mg, 66%).

^{1}H NMR (500 MHz, Methanol-cf$_4$), δ_H ppm: 9.06 (d, J=1.3 Hz, 1H), 8.74 (s, 1H), 8.42 (d, *J*=6.0 Hz, 1H), 8.34 (dd, *J=2.6,* 1.5 Hz, 1H), 8.19 (d, *J=2.7* Hz, 1H), 7.72 (dd, *J*=6.0, 1.0 Hz, 1H).

LCMS (ES): Found 174.0 $[M+H]^+$.

NaH (60%, 48.5mg, 1.21mmol) was added to a solution of **(3)** (200mg, 1.15mmol) in DMF (7mL) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)benzoate (344mg, 1.5mmol) was added as a solution in DMF (3ml_), the stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100ml_). Brine (25ml_) was added and the aqueous was extracted with EtOAc (2 x 100ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Purification by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) yielded **(4)** (187mg, 50%).

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.85 (d, *J*=1.4 Hz, 1H), 8.77-8.80 (m, 1H), 8.34-8.38 (m, 2H), 8.29 (d, *J=2.6* Hz, 1H), 7.95 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 6.91 (dd, J^6.0, 1.2 Hz, 1H), 5.49 (s, 2H), 3.87 (s, 3H).

LCMS (ES): Found 322.0 $[M+H]^+$.

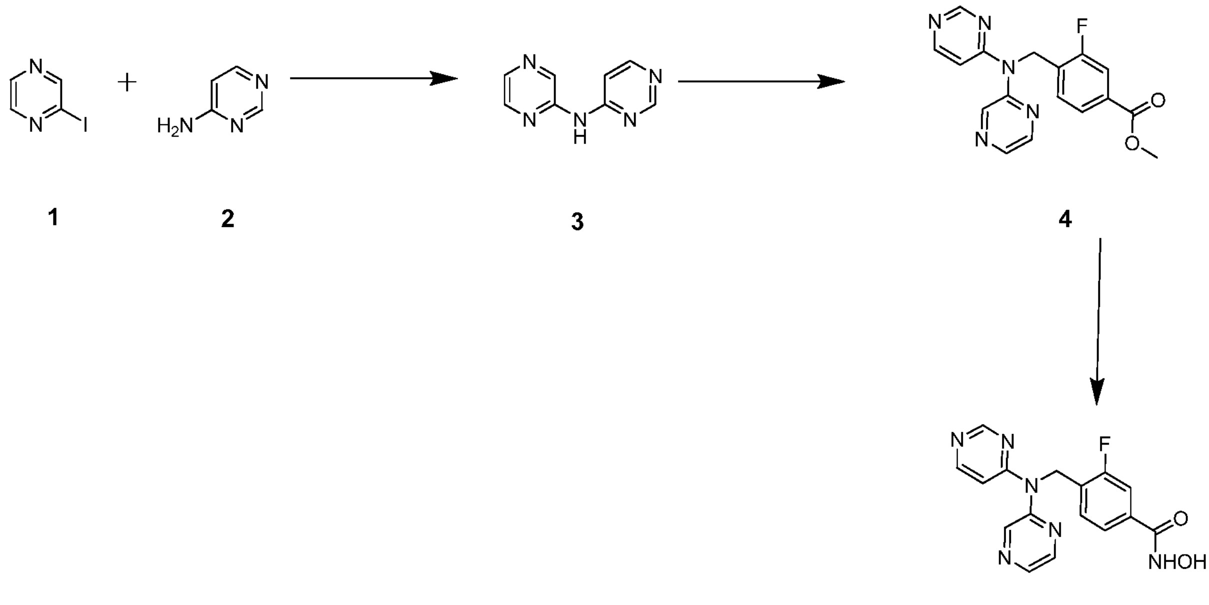
A solution of **(4)** (0.09ml_, 0.58mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at rt for 40h. Solvent was removed *in vacuo* and the residue purified by reverse phase HPLC to give **Example DD** (30mg,15%).

^{1}H NMR (500 MHz, Methanol-cf$_4$), δ_H ppm: 8.89 (d, J=1.4 Hz, 1H), 8.69 (s, 1H), 8.47 (dd, J^2.5, 1.5 Hz, 1H), 8.25-8.37 (m, 2H), 7.68 (d, *J*=8.3 Hz, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.08 (dd, J^6.2, 1.2 Hz, 1H), 5.51 (s, 2H).

LCMS (ES): Found 323.0 $[M+H]^+$.

Example EE

N-Hydroxy-4-{[(pyrazin-2-yl)(pyrimidin-4-yl)amino]methyl}benzamide



1 2 3 4

EE

NaH (60%, 48.5mg, 1.21 mmol) was added to a solution of **(3)** (200mg, 1.15mmol) in DMF (7ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)-3-fluorobenzoate (371 mg, 1.5mmol) was added as a solution in DMF (3ml_). The stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100ml_). Brine (25ml_) was added and the aqueous was extracted with EtOAc (2 x 100ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* Purification by flash column chromatography with EtOAc/CH_2Cl_2 (0:1-1 :0) then EtOAc/MeOH (1:0-4:1) yielded **(4)** (158mg, 40%).
^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.87 (d, *J*=1.4 Hz, 1H), 8.76-8.78 (m, 1H), 8.36-8.40 (m, 2H), 8.31 (d, *J=2.6* Hz, 1H), 7.69 (d, *J=9.2* Hz, 2H), 7.30 (t, *J*=7.6 Hz, 1H), 6.92 (dd, *J*=6.1, 1.2 Hz, 1H), 5.50 (s, 2H), 3.87 (s, 3H).
LCMS (ES): Found 340.0 $[M+H]^+$.

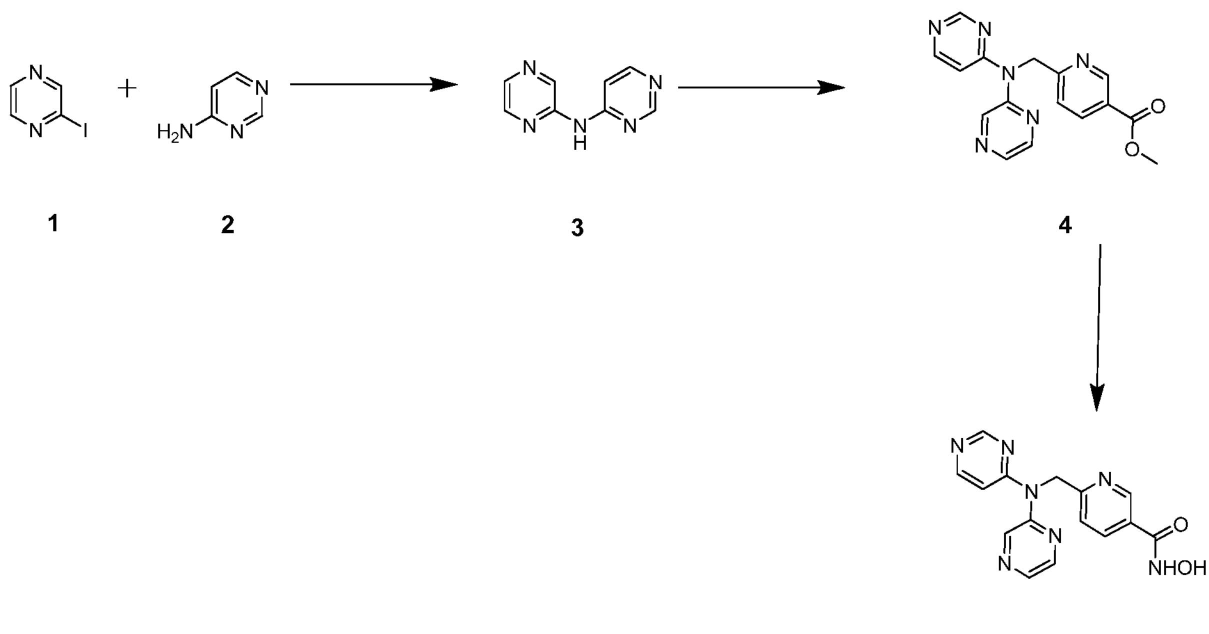
A solution of **(4)** (0.08 mL, 0.47 mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at rt for 18 h. Solvent was concentrated to dryness and the residue purified by neutral pH reverse phase HPLC to give **Example EE** (25mg, 15%).

^{1}H NMR (500 MHz, Methanol-cf_4), δ_H ppm: 8.91 (d, J=1.4 Hz, 1H), 8.70 (s, 1H), 8.48 (dd, *J=2.5,* 1.5 Hz, 1H), 8.31-8.38 (m, 2H), 7.43-7.50 (m, 2H), 7.35 (t, *J*=7.9 Hz, 1H), 7.09 (dd, J^6.2, 1.2 Hz, 1H), 5.53 (s, 2H).

LCMS (ES): Found 341 .0 $[M+H]^+$.

Example FF

N-Hydroxy-6-{[(pyrazin-2-yl)(pyrimidin-4-yl)amino]methyl}pyridine-3-carboxamide



FF

NaH (60%, 48.5 mg, 1.21 mmol) was added to a solution of **(3)** (200 mg, 1.15mmol) in DMF (7ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 6-(bromomethyl)pyridine-3-carboxylate (345mg, 1.5mmol) was added as a solution in DMF (3ml_). The stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100ml_). Brine (25mL) was added and the aqueous was extracted with EtOAc (2 x 100ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then CH_2Cl_2/MeOH (1:0-4:1) to yield **(4)** (116 mg, 27%).

^{1}H NMR (500 MHz, Chloroform-cO, δ_H ppm: 9.11 (d, *J*=1.6 Hz, 1H), 8.97 (d, J=1.4 Hz, 1H), 8.70-8.77 (m, 1H), 8.34-8.40 (m, 2H), 8.31 (d, *J=2.6* Hz, 1H), 8.18 (dd, J^8.2, 2.1 Hz, 1H), 7.36 (d, *J*=8.2 Hz, 1H), 7.01 (dd, *J*=6.1, 1.2 Hz, 1H), 5.56 (s, 2H), 3.90 (s, 3H).

LCMS (ES): Found 322.9 $[M+H]^+$.

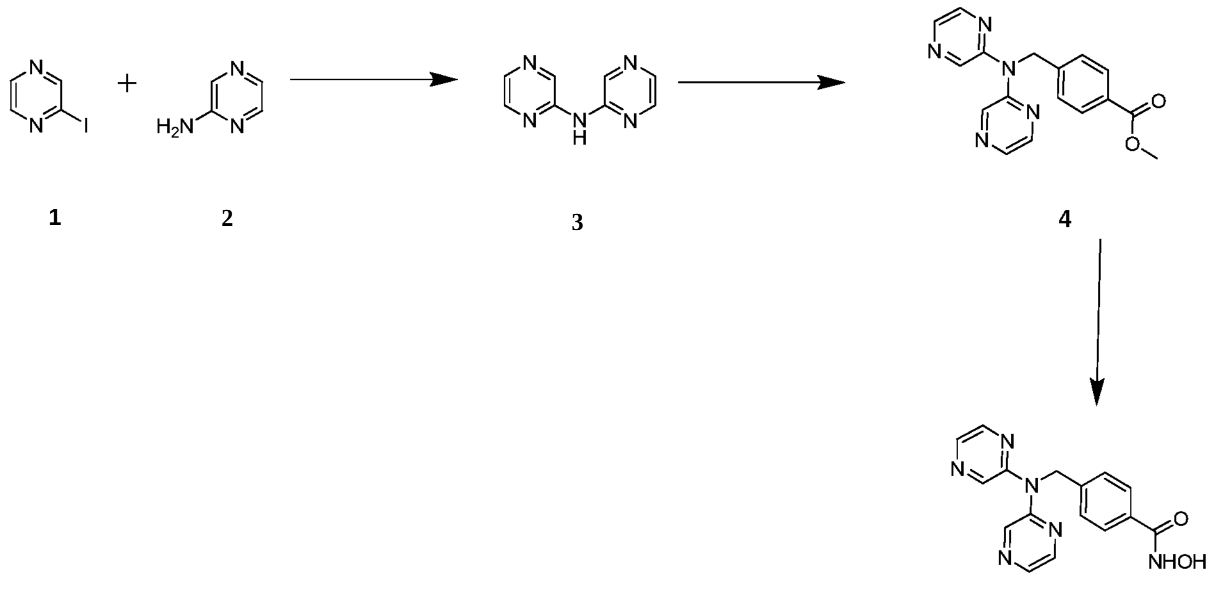
A solution of **(4)** (0.06 mL, 0.31 mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at rt for 18h. The reaction mixture was concentrated to dryness. The residue was purified by reverse phase HPLC to give **Example FF** (25.7 mg, 26%).

^{1}H NMR (500 MHz, DMSO-d_6), δ_H ppm: 8.99 (d, *J*=4.9 Hz, 1H), 8.64-8.76 (m, 2H), 8.32-8.51 (m, 3H), 7.82-7.93 (m, 1H), 7.03-7.30 (m, 2H), 5.45 (m, 2H).

LCMS (ES): Found 324.1 $[M+H]^+$.

Example GG

4-{[Bis(pyrazin-2-yl)amino]methyl}-N-hydroxybenzamide



1 **2** **3** **4**

GG

A solution of 2-iodopyrazine **(1)** (1.2g, 5.83mmol), pyrazin-2-amine **(2)** (609mg, 6.4mmol), Cs_2C0_3 (3.80g, 11.7mmol) and Xantphos (148mg, 0.26mmol) in dioxane (25mL) was purged with N_2(g) for 10min. $Pd_2(dba)_3$ (107mg, 0.12mmol) was added and mixture was heated to 90°C for 3h. Reaction cooled to rt and poured onto water (200ml_), extracted with EtOAc (2 x 150ml_) and CH_2Cl_2-IPA (150ml_, 4:1). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* Flash column chromatography with heptane/EtOAc (4:1-0:1) then EtOAc/MeOH (1:0-3:1) yielded **(3)** as an off white solid (210 mg, 51%).

^{1}H NMR (500 MHz, Chloroform-cO, δ_H ppm: 8.99 (d, J=1.4 Hz, 2H), 8.30 (dd, J^2.6, 1.5 Hz, 2H), 8.1 1 (d, *J=2.7* Hz, 2H).

LCMS (ES): Found 174.1 $[M+H]^+$.

NaH (60%, 48.5mg, 1.21mmol) was added to a solution of **(3)** (200mg, 1.15mmol) in DMF (7ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)benzoate (344mg, 1.5mmol) was added as a solution in DMF (3ml_). The stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100ml_). Brine (25ml_) was added and extracted with EtOAc (2 x

100ml_). Combined organic was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to give **(4)** (196 mg, 53%).

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.59-8.65 (m, 2H), 8.23-8.26 (m, 2H), 8.16 (d, *J=2.5* Hz, 2H), 7.94 (d, *J*=8.3 Hz, 2H), 7.38 (d, *J*=8.2 Hz, 2H), 5.50 (s, 2H), 3.86 (s, 3H).

LCMS (ES): Found 321.9 [M+H]$^+$.

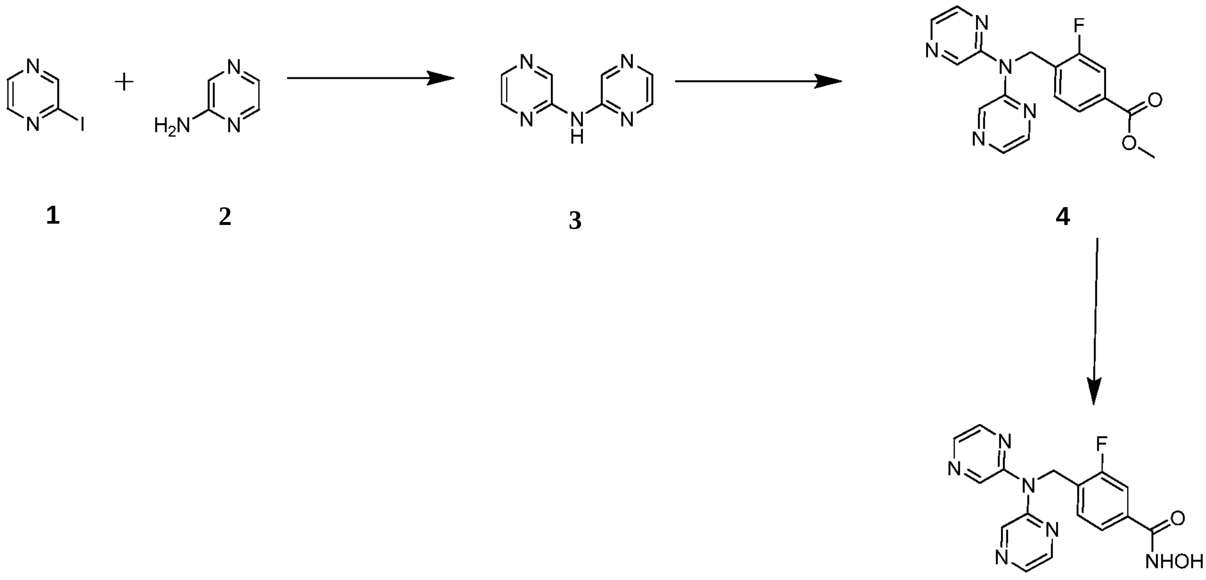
A solution of **(4)** (0.09ml_, 0.61 mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at rt for 72h. Solvent concentrated to dryness and the residue purified by reverse phase HPLC to give **Example GG** (23 mg, 12%).

^{1}H NMR (500 MHz, Methanol-^), δ_H ppm: 8.66 (d, J=1.3 Hz, 2H), 8.28-8.36 (m, 2H), 8.16 (d, *J=2.6* Hz, 2H), 7.67 (d, *J*=8.2 Hz, 2H), 7.45 (d, *J*=8.2 Hz, 2H), 5.56 (s, 2H).

LCMS (ES): Found 323.1 [M+H]$^+$.

Example HH

4-{[Bis(pyrazin-2-yl)amino]methyl}-3-fluoro-N-hydroxybenzamide



1 2 3 4

HH

NaH (60%, 49mg, 1.21mmol) was added to a solution of **(3)** (200 mg, 1.15mmol) in DMF (7mL) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)-3-fluorobenzoate (371 mg, 1.5mmol) was added as a solution in DMF (3mL). The stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100mL). Brine (25mL) was added and the aqueous was extracted with EtOAc (2 x 100mL). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* Purification by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) yielded **(4)** (195mg, 50%).

^{1}H NMR (500 MHz, Chloroform-cO, δ_H ppm: 8.65 (d, J=1.4 Hz, 2H), 8.25 (dd, J^2.5, 1.5 Hz, 2H), 8.18 (d, *J=2.6* Hz, 2H), 7.65-7.72 (m, 2H), 7.31 (t, *J*=7.8 Hz, 1H), 5.53 (s, 2H), 3.87 (s, 3H).

LCMS (ES): Found 339.9 [M+H]$^+$.

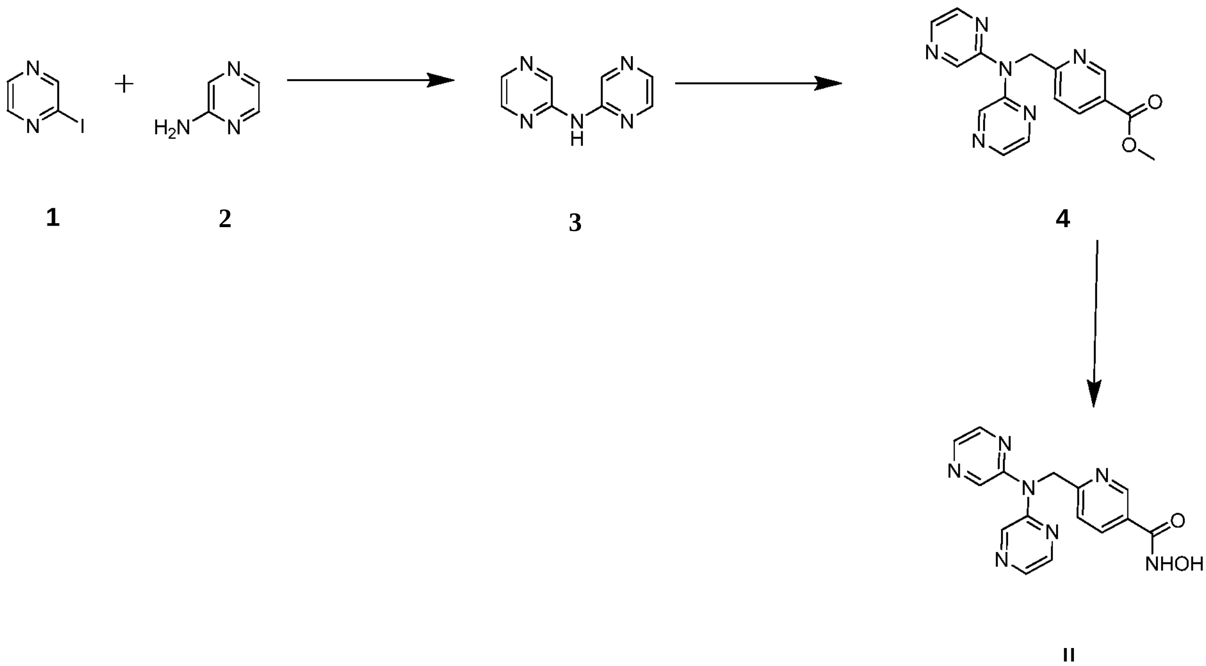
A solution of **(4)** (0.09ml_, 0.57mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 18h. Solvent was concentrated *in vacuo* and the residue purified by reverse phase HPLC to give **Example HH** (81 mg, 41%).

^{1}H NMR (500 MHz, DMSO-d_6), δ_H ppm: 8.76 (d, J=1.4 Hz, 2H), 8.34 (dd, J^2.5, 1.5 Hz, 2H), 8.25 (d, *J=2.6* Hz, 2H), 7.51 (dd, ^=1 1.1 , 1.3 Hz, 1H), 7.45 (dd, J^8.0, 1.4 Hz, 1H), 7.34 (t, *J*=7.8 Hz, 1H), 5.50 (s, 2H).

LCMS (ES): Found 341 .1 [M+H]$^+$.

Example II

6-{[Bis(pyrazin-2-yl)amino]methyl}-N-hydroxypyridine-3-carboxamide



NaH (60%, 48.5mg, 1.21mmol) was added to a solution of **(3)** (200mg, 1.15mmol) in DMF (7ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 6-(bromomethyl)pyridine-3-carboxylate (345mg, 1.5mmol) was added as a solution in DMF (3ml_). The stirring was continued at 70°C for 1h. Reaction cooled to rt and poured onto water (100ml_). Brine (25ml_) was added and the aqueous was extracted with EtOAc (2 x 100ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to give **(4)** (129mg, 35%).

[1]H NMR (500 MHz, Chloroform-cO, δ_H ppm: 9.04-9.13 (m, 1H), 8.70 (s, 2H), 8.19 (s, 2H), 8.13 (dd, J^5.6, 2.3 Hz, 3H), 7.32 (d, *J*=8.2 Hz, 1H), 5.55 (s, 2H), 3.86 (s, 3H).
LCMS (ES): Found 322.9 $[M+H]^+$.

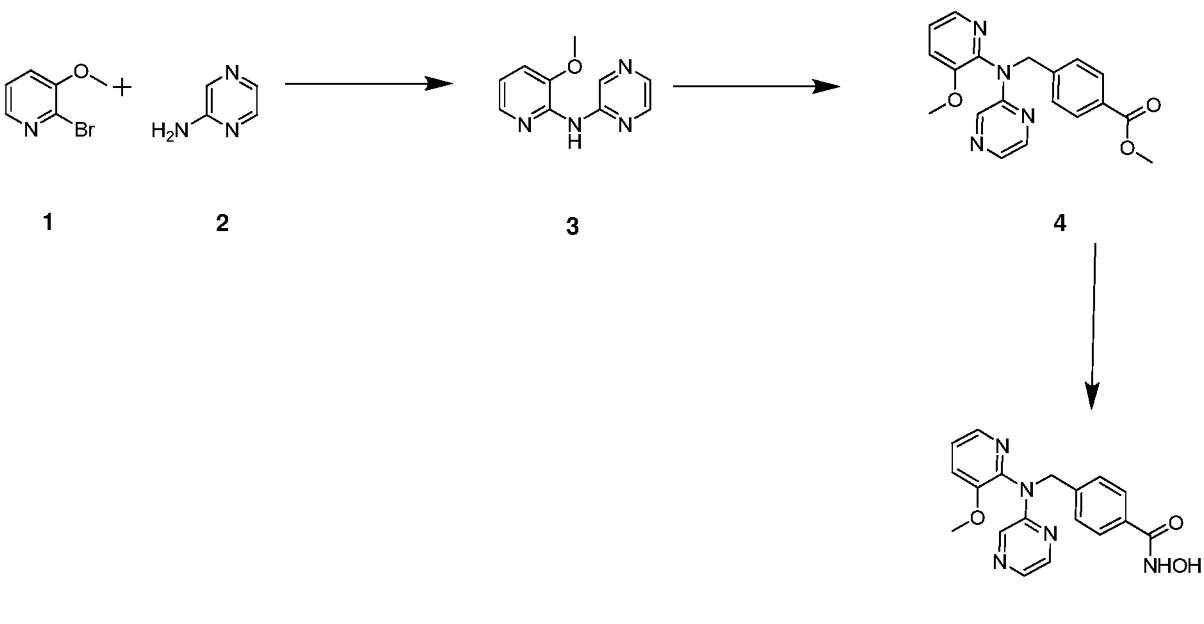
A solution of **(4)** (0.06ml_, 0.4mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 18h. The solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example II** (37mg, 28%).

[1]H NMR (500 MHz, DMSO-*d*6), δ_H ppm: 8.75 (d, J=1.3 Hz, 3H), 8.31 (dd, J^2.6, 1.5 Hz, 2H), 8.21 (d, *J=2.6* Hz, 2H), 7.89 (dd, ^=8.1 , 2.0 Hz, 1H), 7.18 (d, J=8.1 Hz, 1H), 5.47 (s, 2H).

LCMS (ES): Found 324.1 $[M+H]^+$.

Example JJ

N-Hydroxy-4-{[(3-methoxypyridin-2-yl)(pyrazin-2-yl)amino]methyl}benzamide



1 2 3 4

JJ

A solution of pyrazin-2-amine **(2)** (557mg, 5.85mmol), 2-bromo-3-methoxypyridine **(1)** (1.0g, 5.32mmol), Cs_2C0_3 (3.47g, 10.64mmol) and Xantphos (135mg, 0.23mmol) in dioxane (15mL) was purged with N_2(g) for 10min. $Pd_2(dba)_3$ (97.4mg, 0.1 1mmol) was added and the mixture was heated to 90°C for 3h. The reaction was cooled to rt, partitioned between water (200ml_) and EtOAc (200ml_). Phases were separated and aqueous layer was washed with EtOAc (200+100+50ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography eluted with a gradient of CH_2Cl_2/EtOAc (1:0-0:1) to yield **(3)** (1.0g, 88%).

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 9.91 (d, *J*=1.2 Hz, 1H), 8.11-8.20 (m, 2H), 7.91 (dd, *J*=5.0, 1.4 Hz, 1H), 7.80 (s, 1H), 7.06 (dd, J^7.9, 1.3 Hz, 1H), 6.85 (dd, J^7.9, 5.0 Hz, 1H), 3.92 (s, 3H).

LCMS (ES): Found 203.2 $[M+H]^+$.

NaH (60%, 41.5mg, 1.04mmol) was added to a solution of **(3)** (200mg, 0.99mmol) in DMF (10ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20 min then methyl 4-(bromomethyl)benzoate (294mg, 1.29mmol) was added. The stirring was continued at 70°C under N_2(g) for 1h. The reaction was cooled to rt and poured onto water (150ml_) and brine (50ml_), the aqueous was extracted with EtOAc (3 x 100ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to yield **(4)** (251 mg, 73%).

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.06-8.10 (m, 2H), 7.87-7.92 (m, 3H), 7.78 (d, J=1.5 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 2H), 7.23 (dd, J^8.2, 1.4 Hz, 1H), 7.15 (dd, *J*=8.1, 4.7 Hz, 1H), 5.42 (s, 2H), 3.85 (s, 3H), 3.73 (s, 3H).

LCMS (ES): Found 350.9 $[M+H]^+$.

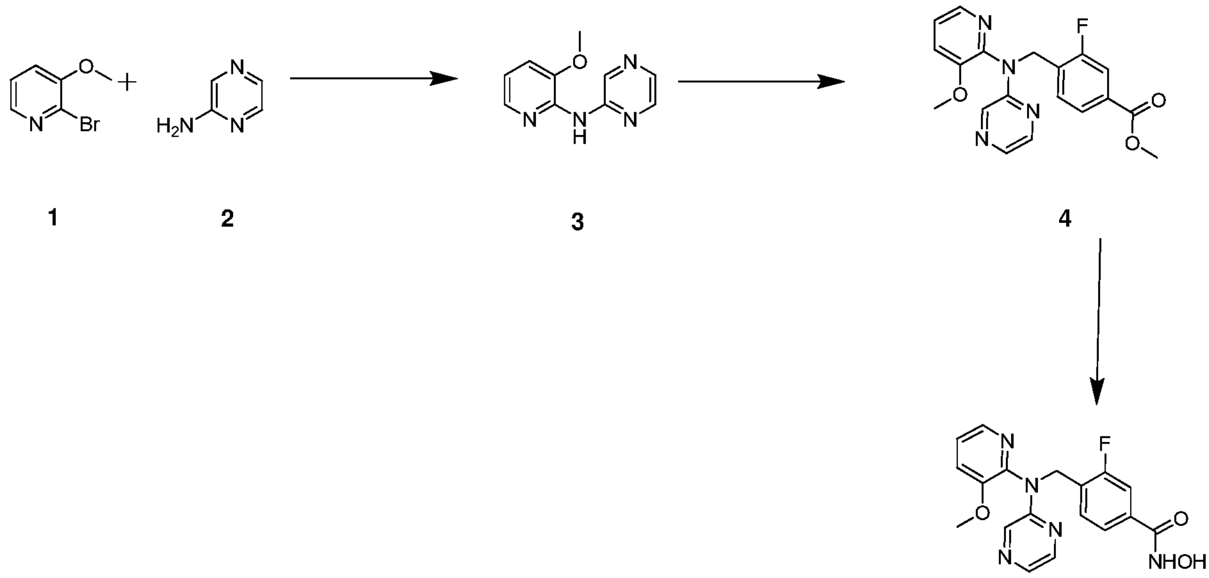
A solution of **(4)** (251 mg, 0.72mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 72h. The solvent concentrated to dryness and the residue purified by reverse HPLC to give **Example JJ** (101mg, 40%) as a beige solid.

^{1}H NMR (500 MHz, DMSO-*d*$_6$), δ_H ppm: 8.11 (dd, J^2.6, 1.6 Hz, 1H), 8.07 (dd, *J=4.7,* 1.3 Hz, 1H), 7.93 (d, *J=2.7* Hz, 1H), 7.79 (d, J=1.4 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 2H), 7.58 (dd, J^8.2, 1.2 Hz, 1H), 7.38 (d, *J*=8.2 Hz, 2H), 7.32 (dd, J^8.2, 4.7 Hz, 1H), 5.30 (s, 2H), 3.76 (s, 3H).

LCMS (ES): Found 352.1 $[M+H]^+$.

Example KK

3-Fluoro-N-hydroxy-4-{[(3-methoxypyridin-2-yl)(pyrazin-2-yl)amino]methyl}benzamide



KK

NaH (60%, 41.5mg, 1.04mmol) was added to a solution of **(3)** (200mg, 0.99mmol) in DMF (10ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)-3-fluorobenzoate (318mg, 1.29mmol) was added. The stirring was continued at 70°C under N_2(g) for 1h. The reaction cooled to rt and poured onto water (150ml_) and brine (50ml_), the aqueous extracted with EtOAc (3 x 100ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to give **(4)** (269mg, 74%).

^{1}H NMR (500 MHz, Chloroform-cO, δ_H ppm: 8.09 (dd, *J=4.7,* 1.4 Hz, 1H), 8.06 (dd, *J=2.6,* 1.6 Hz, 1H), 7.90 (d, *J*=2.7 Hz, 1H), 7.80 (d, J=1.3 Hz, 1H), 7.68 (dd, *J*=8.0, 1.4 Hz, 1H), 7.62 (dd, *J*=10.5, 1.4 Hz, 1H), 7.56 (t, *J*=7.7 Hz, 1H), 7.27 (dd, J^8.3, 1.5 Hz, 1H), 7.18 (dd, J^8.2, 4.7 Hz, 1H), 5.43 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H).

LCMS (ES): Found 368.9 $[M+H]^+$.

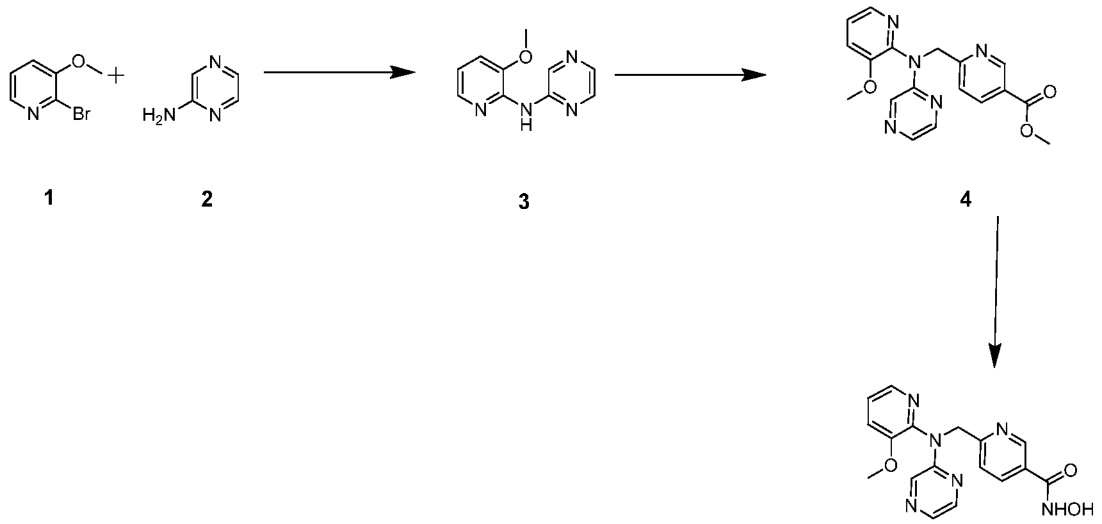
A solution of **(4)** (269mg, 0.73mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 72h. The solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example KK** (93mg, 35%).

^{1}H NMR (500 MHz, DMSO-d_6), δ_H ppm: 8.13 (dd, J^2.6, 1.6 Hz, 1H), 8.08 (dd, *J*=4.7, 1.3 Hz, 1H), 7.95 (d, *J*=2.7 Hz, 1H), 7.80 (d, J=1.3 Hz, 1H), 7.61 (dd, J^8.3, 1.2 Hz, 1H), 7.48-7.43 (m, 3H), 7.35 (dd, J^8.2, 4.7 Hz, 1H), 5.32 (s, 2H), 3.78 (s, 3H).

LCMS (ES): Found 370.1 $[M+H]^+$.

Example LL

N-Hydroxy-6-{[(3-methoxypyridin-2-yl)(pyrazin-2-yl)amino]methyl}pyridine-3-carboxamide



1 2 3 4

LL

NaH (60%, 41.5mg, 1.04mmol) was added to a solution of **(3)** (200mg, 0.99mmol) in DMF (10ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20 min then methyl 6-(bromomethyl)pyridine-3-carboxylate (296mg, 1.29mmol) was added. The stirring was continued at 70°C under N_2(g) for 1h. The reaction was cooled to rt and poured onto water (150ml_) and brine (50ml_) and the aqueous extracted with EtOAc (3 x 100ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to give **(4)** (191mg, 55%).

[1]H NMR (500 MHz, Chloroform-cO, δ_H ppm: 9.07 (d, J=1.9 Hz, 1H), 8.12 (dd, J^8.2, 2.1 Hz, 1H), 8.06 (dd, *J=4.7,* 1.4 Hz, 1H), 8.01 (dd, *J*=2.6, 1.6 Hz, 1H), 7.88 (d, *J*=2.7 Hz, 1H), 7.84 (d, J=1.4 Hz, 1H), 7.54 (d, *J*=8.2 Hz, 1H), 7.27 (dd, J^8.2, 1.4 Hz, 1H), 7.17 (dd, J^8.2, 4.7 Hz, 1H), 5.46 (s, 2H), 3.86 (s, 3H), 3.76 (s, 3H).

LCMS (ES): Found 352.0 $[M+H]^+$.

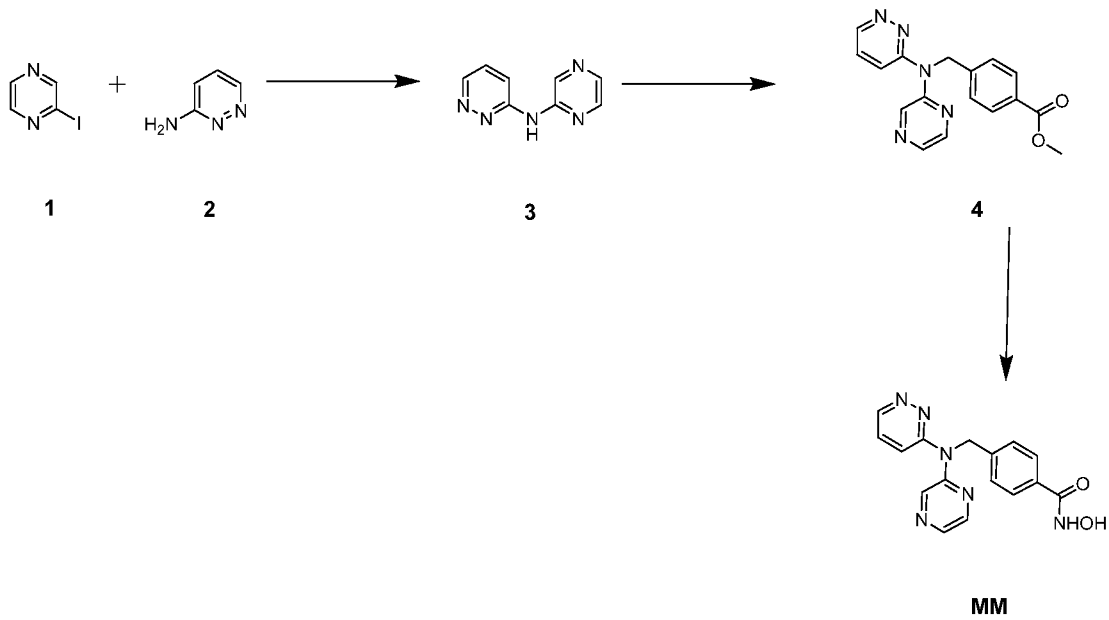
A solution of **(4)** (191mg, 0.54mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 72h. After this time the solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example LL** (35mg, 19%).

[1]H NMR (500 MHz, DMSO-d_6), δ_H ppm: 8.72 (d, *J*=1.8 Hz, 1H), 8.12-8.08 (m, 1H), 8.06 (dd, *J=4.7,* 1.3 Hz, 1H), 7.93 (d, *J=2.7* Hz, 1H), 7.81-7.87 (m, 2H), 7.56-7.61 (m, 1H), 7.32 (dd, *J*=8.2, 4.7 Hz, 1H), 7.25 (d, *J*=8.1 Hz, 1H), 5.29 (s, 2H), 3.77 (s, 3H).

LCMS (ES): Found 353.1 $[M+H]^+$.

Example MM

N-Hydroxy-4-{[(pyrazin-2-yl)(pyridazin-3-yl)amino]methyl}benzamide



A solution of 2-iodopyrazine **(1)** (2.40g, 11.65mmol), pyridazin-3-amine **(2)** (1.2g, 12.82mmol), Cs_2C0_3 (7.6g, 23.3mmol) and Xantphos (297mg, 0.51 mmol) in dioxane (45ml_) was purged with N_2(g) for 10min. $Pd_2(dba)_3$ (214mg, 0.23mmol) in dioxane (5ml_) was added and mixture was heated to 90°C for 3h. The reaction was cooled to rt and partitioned between water (200ml_) and EtOAc (200ml_). The insoluble solid was filtered and put a-side. The phases were separated and aqueous was extracted with EtOAc (200ml_), then CH_2Cl_2-IPA (200ml_, 4:1). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to yield **(3).** The solid [from filtration] was washed with water (100ml_) and triturated with hot MeOH (3x100ml_) and filtered. The filtrates were concentrated to yield a second batch of **(3).** The solid was further washed with water (100ml_) and was sucked dry to yield a third batch of **(3).** All three batches were combined to give **(3)** (1.63g, 80%).

^{1}H NMR (500 MHz, DMSO-d_6), δ_H ppm: 10.49 (s, 1H), 9.00 (d, J=1.2 Hz, 1H), 8.83 (dd, *J=4.6,* 1.2 Hz, 1H), 8.27 (dd, J^2.5, 1.5 Hz, 1H), 8.16 (d, *J=2.7* Hz, 1H), 8.06 (dd, ^=9.1 , 1.2 Hz, 1H), 7.60 (dd, ^=9.1, 4.6 Hz, 1H).

LCMS (ES): Found 174.2 $[M+H]^+$.

NaH (60%, 49mg, 1.21 mmol) was added to a solution of **(3)** (200mg, 1.15mmol) in DMF (8ml_) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)benzoate (344mg, 1.5mmol) in DMF (2ml_) was added. The stirring was continued at 70°C under N_2(g) for 1h. The reaction was cooled to rt, and poured onto water (200ml_) and brine (50ml_) and the aqueous extracted with EtOAc (2 x 150ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with heptane/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) yielded **(4)** (119mg, 32%) as a brown oil.

^{1}H NMR (250 MHz, Chloroform-d), δ_H ppm: 8.85 (dd, *J=4.6,* 1.4 Hz, 1H), 8.56 (d, *J*=1.4 Hz, 1H), 8.25 (dd, J^2.6, 1.5 Hz, 1H), 8.17 (d, *J=2.6* Hz, 1H), 7.89-7.97 (m, 2H), 7.48 (dd, ^=9.1, 1.4 Hz, 1H), 7.42 (d, *J*=8.5 Hz, 2H), 7.33 (dd, ^=9.1 , 4.6 Hz, 1H), 5.64 (s, 2H), 3.86 (s, 3H).

LCMS (ES): Found 321 .0 [M+H]$^+$.

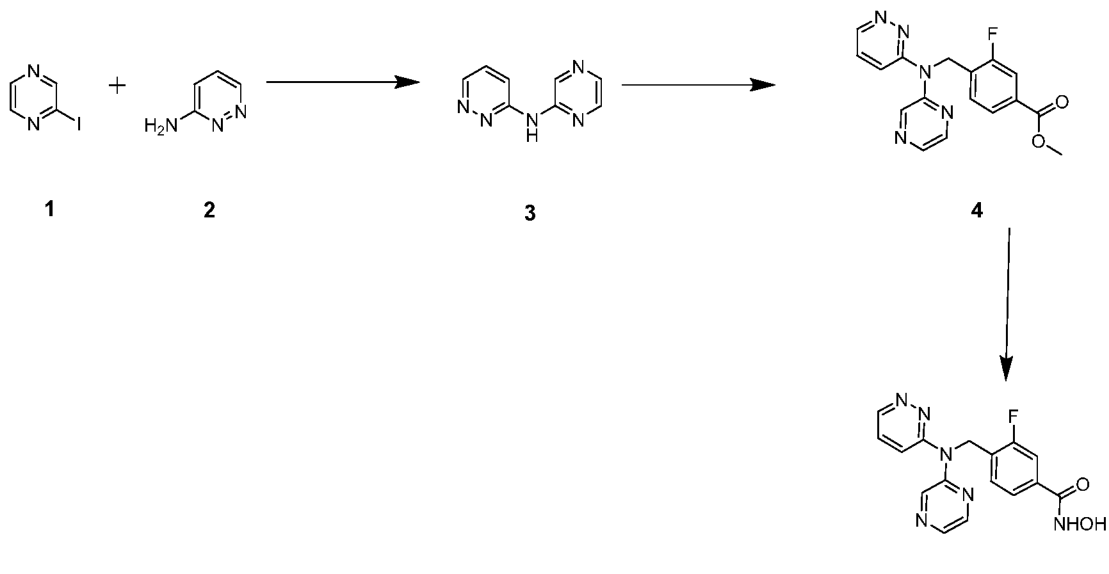
A solution of **(4)** (119mg, 0.37mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 72 h. After this time the solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example MM** (24mg, 20%) as a beige solid.

^{1}H NMR (500 MHz, Methanol-^), δ_H ppm: 8.81 (dd, *J=4.6,* 1.2 Hz, 1H), 8.65 (d, *J*=1.4 Hz, 1H), 8.33 (dd, J^2.6, 1.5 Hz, 1H), 8.16 (d, *J=2.6* Hz, 1H), 7.68 (d, *J*=8.6 Hz, 3H), 7.56 (dd, ^=9.1, 4.6 Hz, 1H), 7.35 (d, *J*=8.2 Hz, 2H), 5.57 (s, 2H).

LCMS (ES): Found 322.2 [M+H]$^+$.

Example NN

3-Fluoro-N-hydroxy-4-{[(pyrazin-2-yl)(pyridazin-3-yl)amino]methyl}benzamide



1 2 3 4

NN

NaH (60%, 73mg, 1.82mmol) was added to a solution of **(3)** (300mg, 1.73mmol) in DMF (11mL) at 5°C under N_2(g). The reaction mixture was stirred for 20min then methyl 4-(bromomethyl)-3-fluorobenzoate (556mg, 2.25mmol) in DMF (4mL) was added. The stirring was continued at 70°C under N_2(g) for 1h. The reaction was cooled to rt and poured onto water (150ml_) and brine (25ml_) and the aqueous extracted with EtOAc (150+100ml_). Combined organic were dried over Na_2S0_4, filtered and concentrated. The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) then EtOAc/MeOH (1:0-4:1) to yield **(4)** (141mg, 24%) as a brown oil.

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.85 (dd, *J=4.6,* 1.3 Hz, 1H), 8.59 (d, *J*=1.4 Hz, 1H), 8.23 (dd, *J=2.6,* 1.5 Hz, 1H), 8.18 (d, *J=2.6* Hz, 1H), 7.61-7.71 (m, 2H), 7.50 (dd, *J*=9.1, 1.3 Hz, 1H), 7.32-7.42 (m, 2H), 5.64 (s, 2H), 3.86 (s, 3H).

LCMS (ES): Found 339.9 $[M+H]^+$.

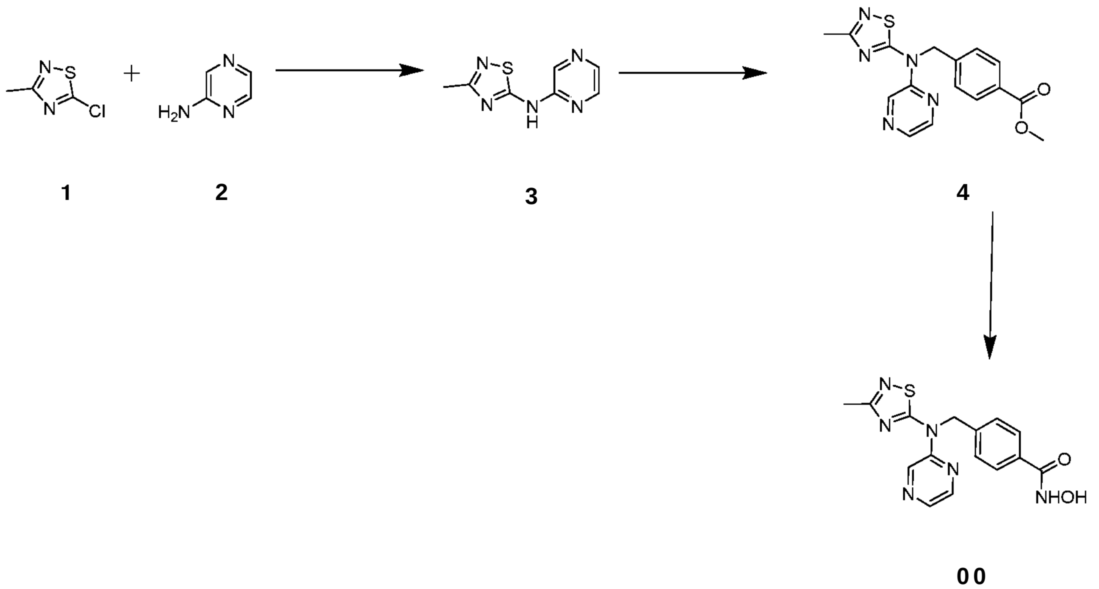
A solution of **(4)** (141 mg, 0.42 mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at rt for 18h. The solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example NN** (51 mg, 36%) as a beige solid.

^{1}H NMR (500 MHz, Methanol-^), δ_H ppm: 8.83 (dd, *J=4.6,* 1.1 Hz, 1H), 8.67 (d, *J*=1.3 Hz, 1H), 8.34 (dd, J^2.5, 1.5 Hz, 1H), 8.18 (d, *J=2.6* Hz, 1H), 7.70 (dd, *J*=9.1, 1.2 Hz, 1H), 7.59 (dd, J^9.1, 4.6 Hz, 1H), 7.47 (d, *J*=11.7 Hz, 2H), 7.32 (t, *J*=8.0 Hz, 1H), 5.60 (s, 2H).

LCMS (ES): Found 341.0 $[M+H]^+$.

Example OO

N-Hydroxy-4-{[(3-methyl-1 ,2,4-thiadiazol-5-yl)(pyrazin-2-yl)amino]methyl}benzamide



NaH (60%, 120mg, 3.3mmol) was added to a solution of **(2)** (140mg, 1.47mmol) in THF (10ml_) under N_2(g). The reaction mixture was stirred for 10min then 5-chloro-3-methyl-1,2,4-thiadiazole **(1)** (190mg, 1.41mmol) was added. The mixture was heated up at 50°C under N_2(g) for 24h.

LCMS (ES): Found 194.0 $[M+H]^+$.

To this mixture was added MeCN (10ml_), methyl 4-(bromomethyl)benzoate (400mg, 1.74mmol) and potassium carbonate (350mg, 1.65mmol). Heating was then continued at 50°C for 2h. Once cooled, the mixture was partitioned between H_20 (10mL) and EtOAc (3 x 20ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with Petrol/EtOAc (1:0-1:1) to yield **(4)** (300mg, 60% over 2 steps) as a white solid.

^{1}H NMR (400 MHz, DMSO-cfe), δ_H ppm: 8.55-8.77 (m, 2H), 8.41 (s, 1H), 7.92 (d, J=7.9 Hz, 2H), 7.39 (d, J=7.9 Hz, 2H), 5.92 (s, 2H), 3.82 (s, 3H), 2.42 (s, 3H).

LCMS (ES): Found 342.0 $[M+H]^+$.

A solution of **(4)** (174 mg, 0.51 mmol) in 0.85M hydroxylamine in MeOH (10 mL) was stirred at 70°C for 8h. The solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example OO** (44mg, 25%).

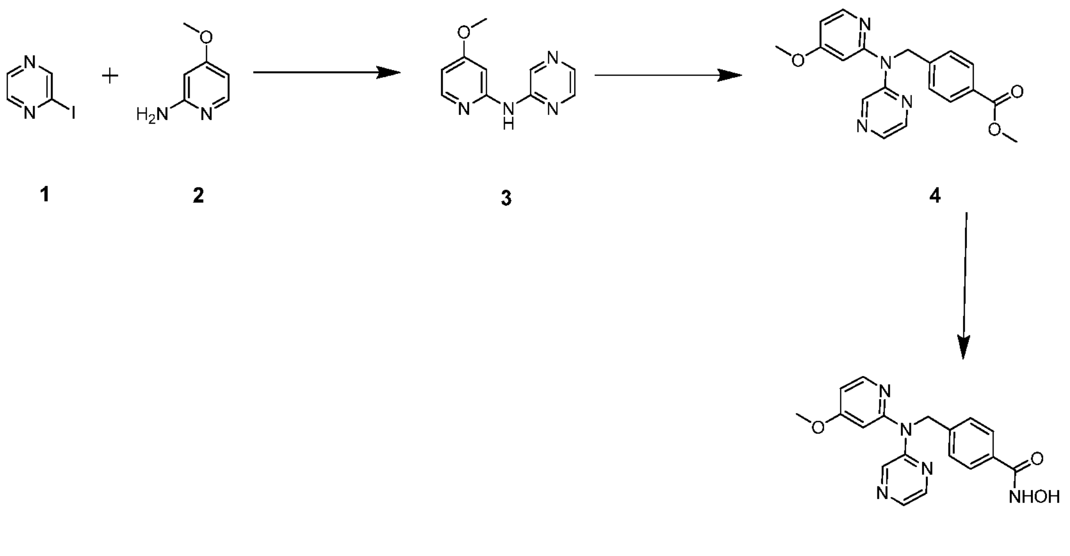
^{1}H NMR (400 MHz, DMSO-cfe), δ_H ppm:

11.45-10.94 (m, 1H), 9.43-8.80 (m, 1H), 8.70 (d, J=1.3 Hz, 1H), 8.61 (dd, *J=2.6,* 1.5 Hz, 1H), 8.40 (d, *J*=2.6 Hz, 1H), 7.70 (d, *J*=8.5 Hz, 2H), 7.31 (d, *J*=8.3 Hz, 2H), 5.88 (s, 2H), 2.43 (s, 3H).

LCMS (ES): Found 343.0 $[M+H]^+$.

Example PP

N-Hydroxy-4-{[(4-methoxypyridin-2-yl)(pyrazin-2-yl)amino]methyl}benzamide



PP

A solution of 2-iodopyrazine **(1)** (1.34g, 6.51 mmol), 4-methoxypyridin-2-amine **(2)** (0.85g, 6.83mmol), Cs_2C0_3 (4.24g, 13.01mmol) and Xantphos (0.17g, 0.29mmol) in dioxane (22ml_) was purged with N_2(g) for 10min then $Pd_2(dba)_3$ (0.12g, 0.13mmol) was added, re-purged for ~5min and reaction was heated to 90°C for 4h. Once cooled down to rt, the mixture was partitioned between H_20 (150ml_) and EtOAc (3 x 120ml_). Combined organics were dried over Na_2S0_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (9:1-0:1) to yield **(3)** (809mg, 61%) as a yellow solid.

^{1}H NMR (500 MHz, Chloroform-d), δ_H ppm: 8.70 (d, *J*=1.3 Hz, 1H), 8.1 1-8.22 (m, 3H), 8.08 (d, *J=2.7* Hz, 1H), 7.43 (d, *J=2.2* Hz, 1H), 6.52 (dd, J^5.8, 2.3 Hz, 1H), 3.88 (s, 3H).

LCMS (ES): Found 203.2 $[M+H]^+$.

NaH (60%, 42mg, 1.04mmol) was added to a solution of **(3)** (200mg, 0.99mmol) in DMF (7ml_) at rt under N_2(g). The reaction mixture was stirred for 30min then methyl 4-(bromomethyl)-3-fluorobenzoate (249mg, 1.09mmol) in DMF (2ml_) was added. The reaction was heated up to 70°C under N_2(g) for 2h, then at rt overnight. The reaction was cooled to rt and partitioned between H_20 (150ml_) and EtOAc (2 x

100ml_). Combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography with CH_2Cl_2/EtOAc (1:0-0:1) to yield **(4)** (173mg, 50%) as a viscous oil.

^{1}H NMR (300 MHz, Chloroform-d), δ_H ppm: 8.63 (dd, J=1.4 Hz, 1H), 8.14-8.22 (m, 2H), 8.01 (d, *J=2.6* Hz, 1H), 7.92 (d, *J*=8.2 Hz, 2H), 7.39 (d, *J*=8.2 Hz, 2H), 6.61 (d, *J*=*2*.1 Hz, 1H), 6.54 (dd, J^5.8, 2.2 Hz, 1H), 5.46 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H).

LCMS (ES): Found 350.9 $[M+H]^+$.

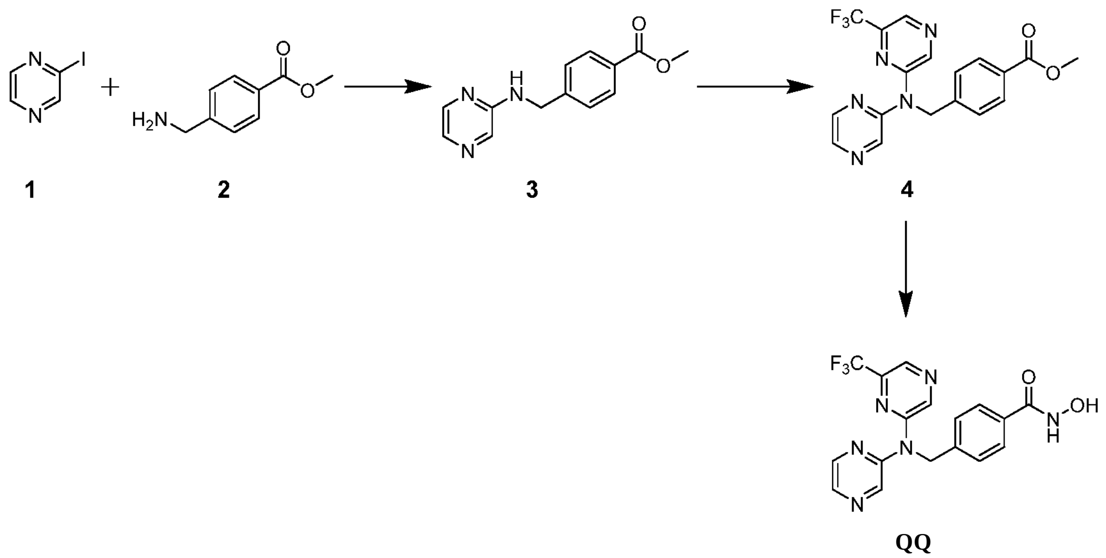
A solution of **(4)** (173mg, 0.49mmol) in 0.85M hydroxylamine in MeOH (10ml_) was stirred at rt for 72h. The solvent was concentrated to dryness and the residue purified by reverse phase HPLC to give **Example PP** (15mg, 9%).

^{1}H NMR (500 MHz, Methanol-cf$_4$), δ_H ppm: 8.46 (d, *J*=1.4 Hz, 1H), 8.24 (dd, *J=2.6,* 1.5 Hz, 1H), 8.14 (d, *J*=5.9 Hz, 1H), 8.00 (d, *J=2.7* Hz, 1H), 7.65 (d, *J*=8.3 Hz, 2H), 7.42 (d, *J*=8.3 Hz, 2H), 6.79 (d, *J=2.2* Hz, 1H), 6.73 (dd, J^5.9, 2.2 Hz, 1H), 5.45 (s, 2H), 3.82 (s, 3H).

LCMS (ES): Found 352.0 $[M+H]^+$.

Example QQ

N-Hydroxy-4-{[(pyrazin-2-yl)[6-(trifluoromethyl)pyrazin-2-yl]amino]methyl}benzamide



To a solution of methyl 4-(aminomethyl)benzoate hydrochloride (1.47g, 7.3mmol) in DMSO (14ml_) was added 2-iodopyrazine (1g, 4.9mmol) followed by K_2CO_3 (1.7g, 12.1mmol) under Ar(g). After 2 min vigorous stirring, CuI (46mg, 0.2mmol) was added and the mixture was left to stir at rt overnight. It was partitioned between EtOAc (150ml_) and 50% brine (50ml_) and the organic layer separated, the aqueous extracted with EtOAc (2 x 15ml_), before the combined organic phase was washed with 50% brine (15ml_), dried ($MgSO_4$), and concentrated *in vacuo.* The residue was purified by flash column chromatography with Hexane/EtOAc (7:3-0:1) to yield **(3)** (670mg, 57%) as a white solid.

^{1}H NMR (300MHz, CHLOROFORM-cO δ_H ppm: 7.76-8.1 1 (m, 5H), 7.43 (d, *J*=8.5 Hz, 2H), 5.01-5.16 (m, 1H), 4.66 (d, *J*=5.8 Hz, 2H), 3.92 (s, 3H).

LCMS (ES): Found 352.0 $[M+H]^+$.

To compound **(2)** (60mg, 0.25mmol), $Pd_2(dba)_3$ (1 1mg, 0.01 mmol), (±)-BINAP (15mg, 0.025mmol) and Cs_2CO_3 (241 mg, 0.74mmol) was added a solution of 2-chloro-6-(trifluoromethyl)pyrazine (90mg, 0.49mmol) in dioxane (2mL) under Ar(g). The reaction mixture was heated at 90°C for 4h then allowed to cool to rt overnight. EtOAc (15ml_), water (4mL) and brine (2ml_) were then added and the organic phase separated, extracting the aqueous with EtOAc (10ml_). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude residue (153mg). The residue was scavenged by dissolving in CH_2Cl_2/MeOH (1:1 , 10ml_) followed by the addition of MP-TMT (370mg, 0.68mmol/g). The mixture was agitated for 24h before filtering off the resin, washing with CH_2Cl_2/MeOH (1:1, 2 x 5ml_). The filtrate was then concentrated *in vacuo* to give crude **(3)** (132mg), as a brown solid which was used directly in the next step.

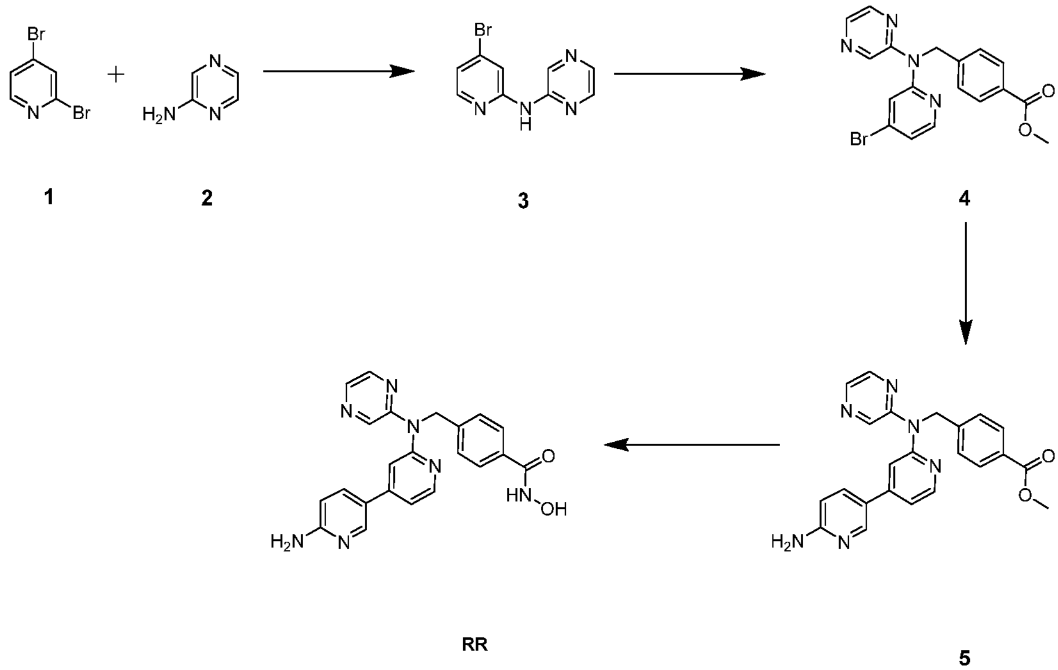
To a solution of crude **(3)** (132mg total, containing maximum 0.25mmol) in THF/MeOH (1:1 , 4ml_) was added NH_2OH solution (50% wt. H_2O , 306µL, 5mmol) followed by NaOH (6M, 83µL, 0.5mmol). After 50 min stirring at rt, $KHSO_4$ (1M, 2ml_), water (5ml_) and CH_2Cl_2 (6ml_) were added. The organic phase was separated and the aqueous extracted with CH_2Cl_2 (2 x 5ml_). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. Purification by reverse phase C-18 chromatography with MeCN/H_2O (19:1-1 :1) gave **Example QQ** (81 mg, 83% over 2 steps) as a light brown solid.

^{1}H NMR (DMSO-d_6) δ_H ppm: 8.93 (s, 1H), 8.88 (d, *J*=1.7 Hz, 1H), 8.62 (s, 1H), 8.42 (dd, J^2.6, 1.5 Hz, 1H), 8.34 (d, *J=2.6* Hz, 1H), 7.62 (d, *J*=8.3 Hz, 2H), 7.27 (d, J=8.3 Hz, 2H), 5.46 (s, 2H).

LCMS (ES): Found 391 .1 $[M+H]^+$.

Example RR

4-({[5-(6-Aminopyridin-3-yl)pyridin-2-yl](pyrazin-2-yl)amino}methyl)-N-hydroxybenzamide



A mixture of 2,4-dibromopyridine **(1)** (5.0g, 21.1mmol), pyrazin-2-amine **(2)** (2.21g, 23.22mmol), Cs_2C0_3 (15.1g, 46.4mmol) and Xantphos (61 1mg, 1.05mmol) was suspended in dioxane (50ml_). The mixture was flushed with N_2(g) for 1min before $Pd_2(dba)_3$ (386mg, 0.422mmol) was added. Mixture was flushed again with N_2(g) and it was heated up to 90°C overnight. Once cooled, the mixture was partitioned between H_20 (150ml_) and EtOAc (3 x 150ml_). The combined organic extracts were washed with brine, dried with $MgS0_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography with heptane/EtOAc (9:1-2:3) to yield **(3)** (2.6g, 49%) as pale yellow solid.

^{1}H NMR (500 MHz, Chloroform-cO, δ_H ppm: 8.74 (d, J=1.3 Hz, 1H), 8.22 (dd, *J=2.6,* 1.5 Hz, 1H), 8.15 (d, *J=2.7* Hz, 1H), 8.1 1 (d, *J*=5.4 Hz, 1H), 8.07 (d, J=1.5 Hz, 1H), 7.63 (s, 1H), 7.10 (dd, J^5.4, 1.6 Hz, 1H).

LCMS (ES): Found 251 .0-253.0 $[M+H]^+$.

To a solution of **(3)** (1.08g, 4.3mmol) in DMF (15ml_) cooled to 0°C under N_2(g) was added NaH (60%, 206mg, 5.16mmol). The mixture was stirred for 30min. Then, a solution of methyl 4-(bromomethyl)benzoate (1.08g, 4.73mmol) in DMF (5mL) was added and the mixture was heated up to 50°C for 1.5h. Once cooled down, the reaction was partitioned between H_20 (150ml_) and EtOAc (3 x 150ml_). The combined organic extracts were washed with brine, dried with $MgS0_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography with heptane/EtOAc (9:1-2:3) to yield **(4)** (915mg, 53%) as white solid.

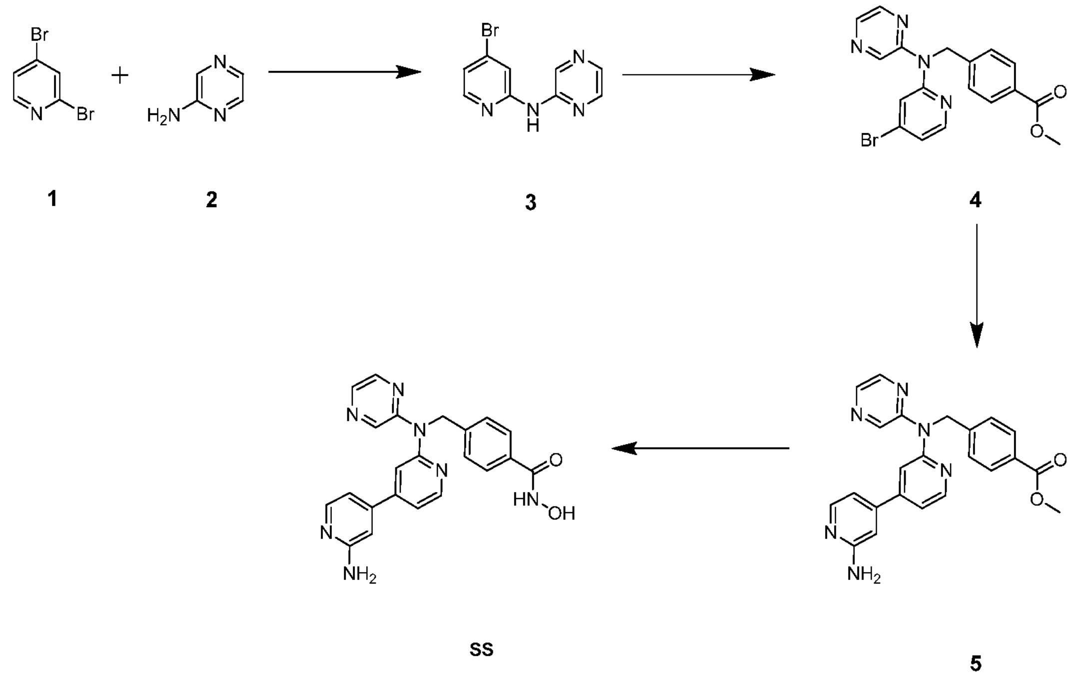
^{1}H NMR (500 MHz, Chloroform-*d*), δ_H ppm: 8.66 (d, *J*=**1.4** Hz, 1H), 8.25 (dd, J^2.5, 1.6 Hz, 1H), 8.15 (d, *J*=5.3 Hz, 1H), 8.13 (d, *J=2.6* Hz, 1H), 7.95 (d, *J*=8.3 Hz, 2H), 7.39 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=**1.4** Hz, 1H), 7.10 (dd, J^5.3, 1.5 Hz, 1H), 5.49 (s, 2H), 3.88 (s, 3H).
LCMS (ES): Found 399.0-401 .0 $[M+H]^+$.

To a suspension of **(4)** (200mg, 0.50mmol), 5-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)pyridin-2-amine (132.3mg, 0.6mmol) and Cs_2C0_3 (326mg, LOmmol) in DMF (4mL) and H_20 (1mL) was added $Pd(PPh_3)_4$ (58mg, 0.05mmol). The mixture was flushed with N_2(g) then it was heated up to 90°C for 2h. Once cooled down, H_20 (20mL) was added and a precipitate was left to settle at rt for 72h. After filtration, washings with H_20 (2ml_) and drying, **(5)** was obtained as a brown solid (219mg, quant.).
^{1}H NMR (500 MHz, Methanol-*d*$_4$), δ_H ppm: 8.54 (s, 1H), 8.31 (d, *J*=5.3 Hz, 1H), 8.25-8.28 (m, 1H), 8.23 (d, *J=2.3* Hz, 1H), 8.02 (d, *J=2.6* Hz, 1H), 7.92 (d, *J*=8.2 Hz, 2H), 7.77 (dd, J^8.8, 2.4 Hz, 1H), 7.50 (s, 1H), 7.48 (d, *J*=5.5 Hz, 2H), 7.32 (d, *J*=5.4 Hz, 1H), 6.65 (d, *J*=8.8 Hz, 1H), 5.55 (s, 2H), 3.86 (s, 3H).
LCMS (ES): Found 413.0 $[M+H]^+$.

A solution of **(5)** (219mg, 0.53mmol) in 0.85M NH_2OH in MeOH (5ml_) was stirred at rt overnight. The volatiles were then removed *in vacuo* and the residue was purified by reverse prep HPLC to give **Example RR** (19mg, 8%) as pale yellow solid.
1H NMR (500 MHz, DMSO-*d*$_6$), δ_H ppm: 8.63 (d, *J*=**1.4** Hz, 1H), 8.35 (d, *J=2.3* Hz, 1H), 8.27-8.28 (m, 1H), 8.26-8.27 (m, 1H), 8.07 (d, *J=2.6* Hz, 1H), 7.76 (d, *J=2.6* Hz, 1H), 7.61 (d, *J*=8.3 Hz, 2H), 7.51 (s, 1H), 7.30 (dd, J^5.3, 1.5 Hz, 1H), 7.26 (d, *J*=8.2 Hz, 2H), 6.52 (d, *J*=8.7 Hz, 1H), 6.36 (s, 2H), 5.45 (s, 2H).
LCMS (ES): Found 414.0 $[M+H]^+$.

Example SS

4-({[5-(2-Aminopyridin-4-yl)pyridin-2-yl](pyrazin-2-yl)amino}methyl)-N-hydroxybenzamide



To a suspension of **(4)** (200mg, 0.50mmol), 4-(4,4,5,5-tetramethyl-1 ,3,2-dioxaborolan-2-yl)pyridin-2-amine (132.3mg, 0.6mmol) and Cs_2C0_3 (326mg, lOmmol) in DMF (4ml_) and H_20 (1ml_) was added $Pd(PPh_3)_4$ (58mg, 0.05mmol). The mixture was flushed with N_2(g) then it was heated up to 90°C for 2h. Once cooled down, H_20 (20ml_) was added and a precipitate was left to settle at rt for 3h. After filtration, washings with H_20 (2ml_) and drying, a pale orange solid was obtained, which was purified by flash column chromatography with heptane/EtOAc (4:1-0:1) then EtOAc/MeOH (1:0-7:3) to give **(5)** (82mg, 40%) as a yellow solid.

1H NMR (500 MHz, Methanol-cf_4), δ_H ppm: 8.60 (s, 1H), 8.41 (d, *J=5.2* Hz, 1H), 8.29 (d, J=1.3 Hz, 1H), 8.06 (d, *J=2.5* Hz, 1H), 7.97 (d, *J=5.4* Hz, 1H), 7.93 (d, *J*=8.3 Hz, 2H), 7.53 (s, 1H), 7.49 (d, J=8.1 Hz, 2H), 7.34 (d, *J*=5.2 Hz, 1H), 6.81-6.84 (m, 1H), 6.81 (s, 1H), 5.58 (s, 2H), 3.86 (s, 3H).

LCMS (ES): Found 413.0 $[M+H]^+$.

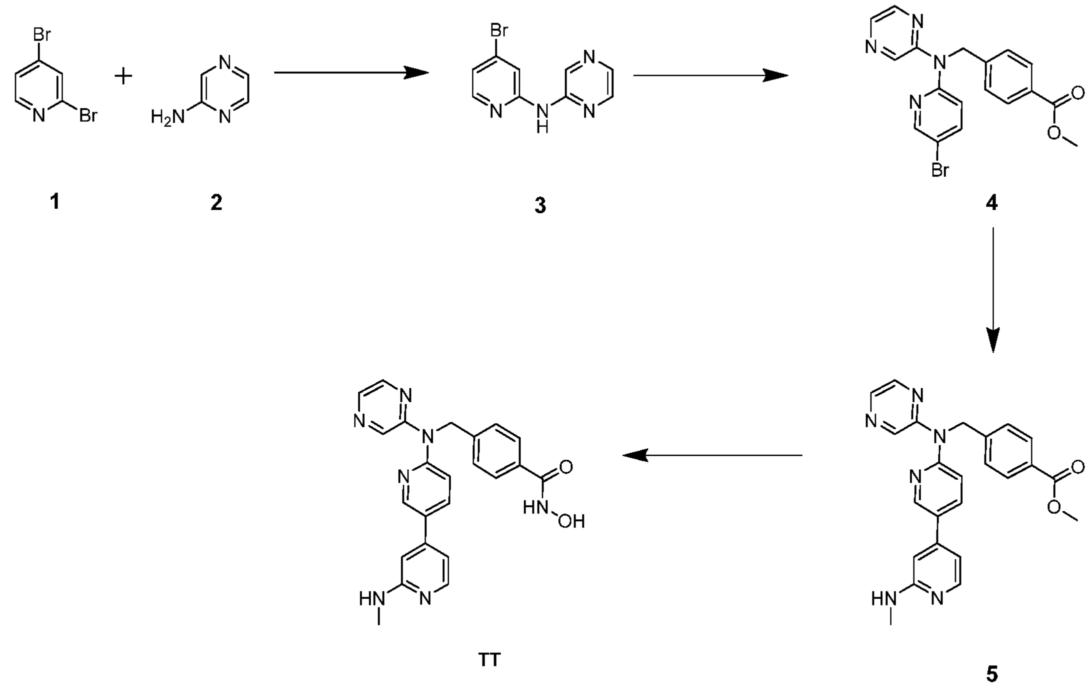
A solution of **(5)** (82mg, 0.20mmol) in 0.85M NH_2OH in MeOH (5mL) was stirred at rt overnight. The volatiles were then removed *in vacuo* and the residue was purified by reverse prep HPLC to give **Example SS** (19mg, 8%) as white solid.

1H NMR (500 MHz, Methanol-^), δ_H ppm: 8.59 (d, *J*=1.4 Hz, 1H), 8.39 (d, *J*=5.2 Hz, 1H), 8.29 (dd, *J=2.7,* 1.5 Hz, 1H), 8.05 (d, *J=2.7* Hz, 1H), 7.97 (d, *J*=5.5 Hz, 1H), 7.66 (d, *J*=8.3 Hz, 2H), 7.49 (s, 1H), 7.45 (d, *J*=8.2 Hz, 2H), 7.32 (dd, J^5.2, 1.2 Hz, 1H), 6.82 (dd, J^5.5, 1.3 Hz, 1H), 6.78 (s, 1H), 5.55 (s, 2H).

LCMS (ES): Found 414.0 $[M+H]^+$.

Example TT

N-hydroxy-4-[({5-[2-(methylamino)pyridin-4-yl]pyridin-2-yl}(pyrazin-2-yl)amino)methyl]benzamide



To a suspension of **(4)** (120mg, 0.3mmol), N-methyl-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (84mg, 0.36mmol) and Cs_2C0_3 (196mg, 0.6mmol) in DMF (2mL) and H_20 (0.5ml_) was added $Pd(PPh_3)_4$ (58mg, 0.05mmol). The mixture was flushed with N_2(g) then it was heated up to 90°C for 4h. Once cooled down, H_20 (10mL) was added and the reaction was stirred for 20 min.

After filtration, washings with MeCN (2ml_) and drying, a black solid was obtained, which was purified by preparative HPLC to give **(5)** (80mg, 59%) as a white solid.

1H NMR (500 MHz, DMSO-d_6), δ_H ppm: 8.70 (d, J=1.4 Hz, 1H), 8.39 (d, *J*=5.2 Hz, 1H), 8.29 (dd, *J=2.6,* 1.5 Hz, 1H), 8.14 (d, *J=2.6* Hz, 1H), 8.07 (d, *J*=5.3 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 2H), 7.54-7.56 (m, 1H), 7.50 (d, *J*=8.3 Hz, 2H), 7.32 (dd, J^5.2, 1.4 Hz, 1H), 6.77 (dd, J^5.3, 1.5 Hz, 1H), 6.65-6.67 (m, 1H), 6.61 (d, *J*=5.2 Hz, 1H), 5.56 (s, 2H), 3.80 (s, 3H), 2.80 (d, *J=4.9* Hz, 3H).

LCMS (ES): Found 427.5 $[M+H]^+$.

To a solution of **(5)** (80mg, 0.20mmol) in MeOH/THF (1:1, 2ml_) was added hydroxylamine (50% w/w in H_20 ; 0.1 1ml_, 3.75mmol) followed by 6N NaOH (63µL,

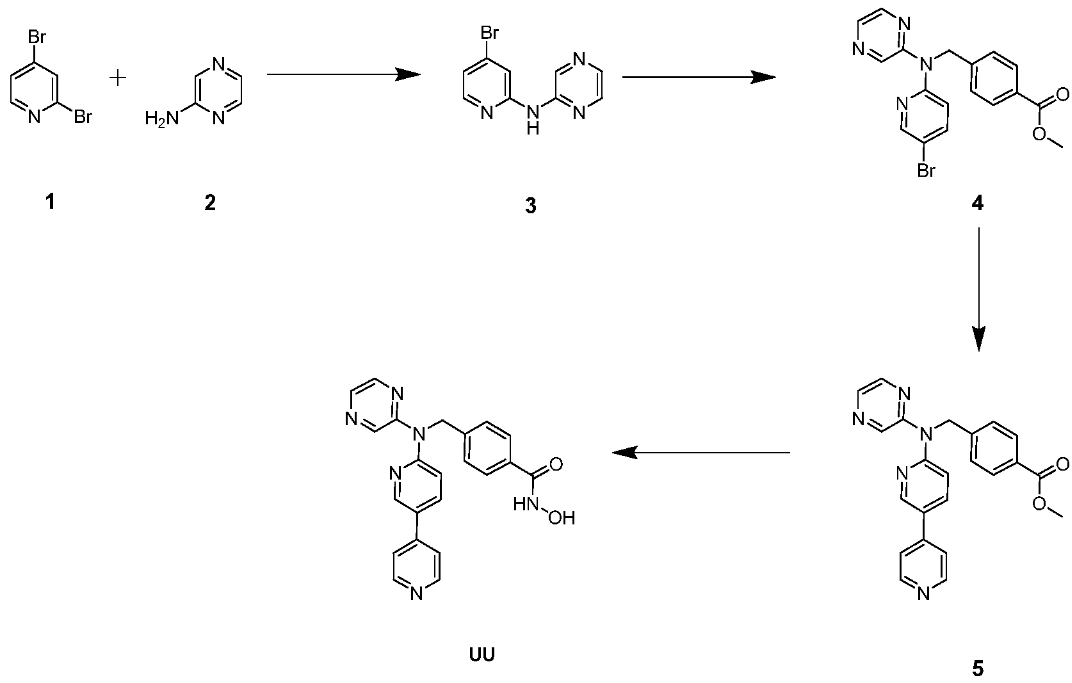
0.38mmol). The mixture was stirred at rt for 3h. Then, 1M $KHSO_4$ (2mL) was added followed by H_2O (6mL). It was extracted with IPA/Chloroform (1:2, 3 x 20ml_).
The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo.* Purification by preparative HPLC yielded **Example TT** (21 mg, 25%) as a pale orange solid.

1H NMR (500 MHz, Methanol-^), δ_H ppm: 11.08 (br.s., 1H), 8.69 (dd, J^6.3, 1.4 Hz, 1H), 8.39 (dd, J^5.0, 1.4 Hz), 8.28-8.32 (m, 1H), 8.13 (dd, J^6.0, 2.6 Hz, 1H), 8.07 (dd, J^5.2, 3.3 Hz, 1H), 7.63-7.67 (m, 1H), 7.58 (d, *J*=8.4 Hz, 1H), 7.53 (m, 1H), 7.42 (d, *J*=8.4 Hz, 1H), 7.36 (d, *J*=8.4 Hz, 1H), 7.31 (ddd, J^8.5, 5.3, 1.4, 1H), 6.65 (ddd, J^8.5, 5.4, 1.5 Hz), 6.66 (d, *J*=9.1 Hz, 1H), 6.58-6.63 (m, 1H), 5.51 (m, 1H), 2.80 (dd, *J=4.8,* 2.9 Hz, 3H).

LCMS (ES): Found 428.2 $[M+H]^+$.

Example UU

N-hydroxy-4-{[(pyrazin-2-yl)[5-(pyridin-4-yl)pyridin-2-yl]amino]methyl}benzamide



To a suspension of **(4)** (120mg, 0.3mmol), (pyridin-4-yl)boronic acid (49mg, 0.36 mmol) and Cs_2CO_3 (196mg, 0.6mmol) in DMF (2ml_) and H_2O (0.5ml_) was added $Pd(PPh_3)_4$ (35mg, 0.03mmol). The mixture was flushed with N_2(g) then it was heated up to 90°C for 4h. Once cooled down, H_2O (10mL) was added and the reaction was stirred for 20 min.

After filtration, a gum was obtained, which was purified by preparative HPLC then SCX column to give **(5)** (82mg, 65%) as a colourless oil.

LCMS (ES): Found 398.5 $[M+H]^+$.

To a solution of **(5)** (82mg, 0.21mmol) in MeOH/THF (1:1, 2ml_) was added hydroxylamine (50% w/w in H_20; 0.15ml_, 0.42mmol) followed by 6N NaOH (80µL, 0.42mmol). The mixture was stirred at rt for 2h.

The volatiles were then removed *in vacuo* and the residue was purified by reverse prep HPLC to give **Example UU** (39mg, 48%) as white solid.

1H NMR (500 MHz, DMSO-d_6), δ_H ppm: 11.05 (br. s., 1H), 8.95 (br. s., 1H), 8.68-8.71 (m, 3H), 8.44 (d, *J*=5.2 Hz, 1H), 8.28-8.31 (m, 1H), 8.14 (d, *J*=2.6 Hz, 1H), 7.72-7.78 (m, 3H), 7.64 (d, *J*=8.2 Hz, 2H), 7.47 (dd, J^5.2, 1.4 Hz, 1H), 7.42 (d, *J*=8.0 Hz, 2H), 5.55 (s, 2H).

LCMS (ES): Found 399.4 $[M+H]^+$.

Biochemical Assay and Data

1) Assay

1. Biochemical Assay Description

Activity against all zinc-dependent HDACs 1 to 11 was assessed by using an acetylated AMC-labeled peptide substrate. The substrate RHKKAc was used for all class I and lib HDACs; for HDAC8, the substrate used was RHKAcKAc. Activity against the class lla HDACs (HDAC4, 5, 7, 9) was determined using a class lla-specific substrate, Acetyl-Lys(trifluoroacetyl)-AMC (Lahm et al, 2007, PNAS, 104, 17335-17340). All assays were based on the AMC-labeled substrate and developer combination.

The protocol involved a two-step reaction: first, the substrate with the acetylated lysine side chain is incubated with a sample containing HDAC activity, to produce the deacetylated products, which are then digested in the second step by the addition of developer to produce the fluorescent signal proportional to the amount of deacetylated substrates.

ii. Enzymes

Human HDAC1 (GenBank Accession No. NM_004964), full length with C-terminal His-tag and C-terminal FLAG-tag, MW= 56 kDa, expressed in baculovirus expression system.

Human HDAC2 (GenBank Accession No. NM_001527), full length with C-terminal His-tag, MW= 56 kDa, expressed inbaculovirus expression system.

Complex of human HDAC3 (GenBank Accession No. NM_003883), full length with C-terminal His tag, MW= 49.7 kDa, and human NCOR2 (amino acid 395-489) (GenBank Accession No.NM_006312), N-terminal GST tag, MW=37.6 kDa, co-expressed in baculovirus expression system.

Human HDAC4 (GenBank Accession No. NM_006037), amino acids627- 1085 with N-terminal GST tag, MW=75.2 kDa, expressed in baculovirus expression system.

Human HDAC5 (GenBank Accession No. NM_005474), full length with N-terminal GST tag, MW= 150 kDa, expressed in baculovirus expression system.

Recombinant human HDAC6 (GenBank Accession No. BC069243), full length, MW=180 kDa, was expressed by baculovirus in Sf9 insect cells using an N-terminal GST tag.

Human HDAC7 (GenBank Accession No. AY302468), (a.a. 518-end) with N-terminal GST tag, MW= 78 kDa, expressed in baculovirus expression system.

Human HDAC8 (GenBankAccession No. NM_018486), full length with C-terminal His tag, MW= 46.4 kDa, expressed in a baculovirus expression system.

Human HDAC9 (GenBank Accession No. NM_178423), amino acids 604-1066 with C-terminal His tag, MW=50.7 kDa, expressed in baculovirus expression system.

Human HDAC10 (a.a. 1-481), GenBank Accession No. NM_032019 with N- terminal GST tag and C-terminal His tag, MW= 78 kDa, expressed in baculovirus expression system.

Human HDAC1 1 (full length) (GenBank Accession No.NM_024827) with N-terminal GST tag, MW= 66 kDa, expressed in baculovirus expression system.

iii. Reaction Conditions

Assay Buffer: 50mM Tris-HCI, pH8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$. Before use, 1mg/ml_ BSA and DMSO are added.

HDAC1 : 2.68 nM HDAC1 and 50m M HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC2: 3.33 nM HDAC2 and 50mM HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC3: 1.13 nM HDAC3 and 50mM HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC6: 0.56 nM HDAC6 and 50mM HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC8: 46.4 nM HDAC8 and 50mM HDAC8 substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC10: 96.15 nM HDAC10 and 50mM HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

HDAC11: 227.27 nM HDAC11 and 50mMHDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 2 hours at 30°C.

For class IIa HDACs, assay buffer is the same.

Other reaction conditions are as follows:

HDAC4: 0.03 nM HDAC4 and 50mM Class IIa HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 30 minutes at room temperature.

HDAC5: 0.67 nM HDAC5 and 50mM Class IIa HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 30 minutes at room temperature.

HDAC7: 0.26 nM HDAC7 and 50mM Class IIa HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 30 minutes at room temperature.

HDAC9: 2.37 nM HDAC9 and 50mM Class IIa HDAC substrate are in the reaction buffer with 1% DMSO final. Incubate for 30 minutes at room temperature.

Control Inhibitor: Trichostatin A (TSA)

Fluorescent Deacetylated Standard: Biomol, Cat#KI-142;

For Standard Control, compound is added at assay concentration to 2.5 uM Fluorescent Deacetylated Standard; 10 doses in 6 uL

For Fluorescence Background Control, compound is added at assay concentrations to 50 mM HDAC substrate; 10 doses in 6 uL.

Fluorescence background signal is then subtracted from compound data signal.

% Conversion must be between 5% and 15% to obtain optimum result.

iv. Assay Procedure

Stage 1: Deacetylation of substrate by incubation of HDAC enzymes with compounds

Stage 2: Development by addition of Developer to digest the deacetylated substrate, and generate the fluorescent color; Detection: 360/460 Ex/Em

2) Inhibition of HDAC enzymes

Example	IC_{50} (nM) HDAC	
	1	6
A	****	*
B	****	*
C	***	*
D	***	*
E	***	*
F	****	*
G	****	*
H	****	*
1	***	*
J	****	*
K	****	*
L	****	*
M	****	*
N	****	*
0	****	*
P	****	*
Q	***	*
R	****	*
S	****	***
T	****	***
u	***	*
V	****	*
w	****	*
X	****	*
Y	****	*
z	****	*
AA	***	*
BB	***	*
CC	****	**
DD	***	*
EE	***	*
FF	****	*
GG	***	*

HH	***	*
II	***	*
JJ	***	*
KK	***	*
LL	****	*
MM	****	*
NN	****	*
0 0	***	*
PP	***	*
RR	***	*
SS	***	*

Key:

**** ≥ 10uM

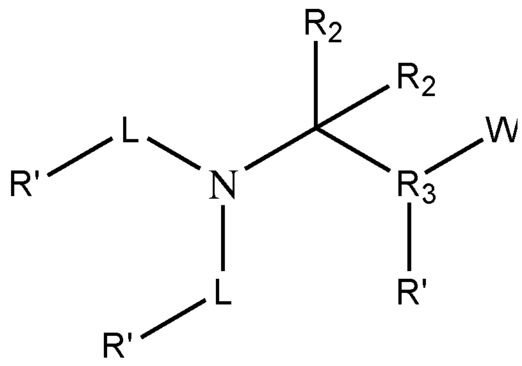
*** ≤ 10uM ≥ 1uM

** ≤ 1uM ≥ 500nM

* ≤ 500nM

CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

each R' is independently selected from H and QRi;

each Q is independently selected from a bond, CO, $C0_2$, NH, S, SO, $S0_2$ or O;

each R_1 is independently selected from H, C_1-C_{10} alkyi, C_2-Ci_0 alkenyl, C_2-Cio alkynyl, aryl, heteroaryl, C_1-C_{10} cycloalkyl, halogen, C_1-C_{10} alkylaryl, C_1-C_{10} alkyi heteroaryl or C_1-C_{10} heterocycloalkyl;

each L is independently selected from a 5 to 10-membered nitrogen-containing heteroaryl;

W is a zinc-binding group;

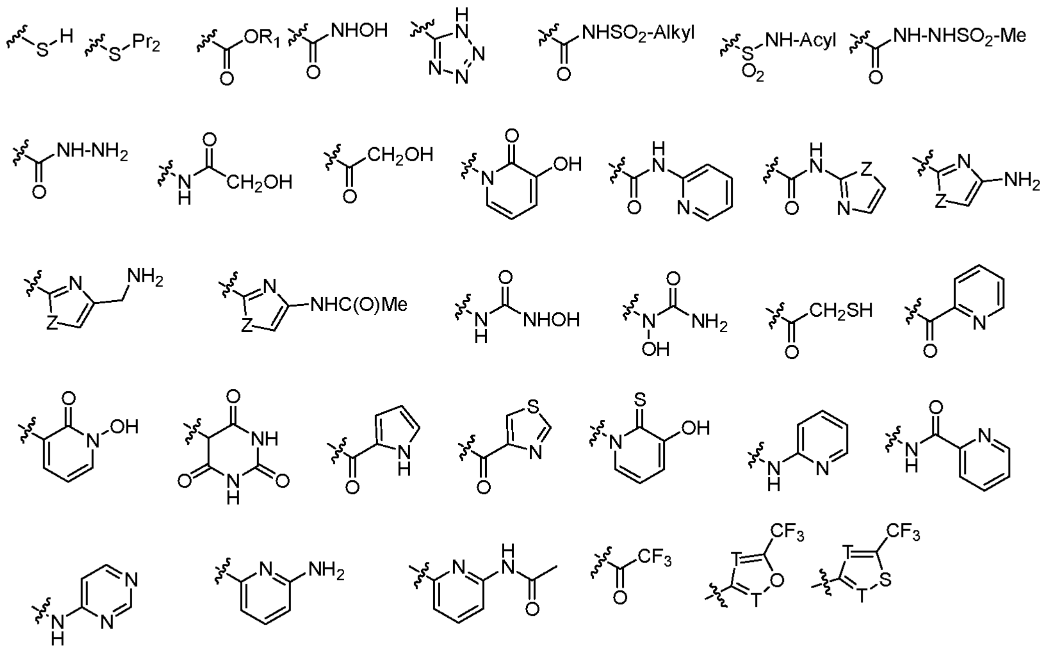
each R_2 is independently hydrogen or C_1 to C_6 alkyi; and

R_3 is an aryl or heteroaryl;

each aryl or heteroaryl may be substituted by up to three substituents selected from C_1-C_6 alkyi, hydroxy, C_1-C_3 hydroxyalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, amino, C_1-C_3 mono alkylamino, C_1-C_3 bis alkylamino, C_1-C_3 acylamino, C_1-C_3 aminoalkyl, mono (C_1-C_3 alkyi) amino C_1-C_3 alkyi, bis(C_1-C_3 alkyi) amino C_1-C_3 alkyi, C_1-C_3-acylamino, C_1-C_3 alkyi suifonyiamino, halo, nitro, cyano, trifluoromethyl, carboxy, C_1-C_3 alkoxycarbonyl, aminocarbonyl, mono C_1-C_3 alkyi aminocarbonyl, bis C_1-C_3 alkyi aminocarbonyl, $-S0_3H$, C_1-C_3 alkylsulfonyl, aminosulfonyl, mono C_1-C_3 alkyi aminosulfonyl and bis C_1-C_3-alkyl aminosulfonyl; and

each alkyi, alkenyl or alkynyl may be substituted with halogen, NH_2, $N0_2$ or hydroxyl.

2. A compound according to claim 1, wherein W is selected from:



wherein $\mathbf{R_1}$ is as defined in claim 1, Pr^2 is H or a thiol protecting group, Z is selected from O, S or NH and T is N or CH.

3. A compound according to claim 2, wherein W is -CONHOH.

4. A compound according to any preceding claim, wherein each L is independently selected from a 5 or 6-membered nitrogen-containing heteroaryl, which is optionally fused to a benzene.

5. A compound according to any preceding claim, wherein in at least one, preferably both L groups, the atom that is directly bonded to the N is a carbon, and at least one nitrogen atom is directly bonded to said carbon.

6. A compound according to any preceding claim, wherein L is independently selected from pyridinyl, pyrimidinyl, pyridazinyl, oxadiazolyl, pyrazolyl, thiadiazolyl, pyrazinyl, benzofused thiazolyl, benzofused oxazolyl or benzofused imidazolyl, preferably, L is independently selected from pyridyl and pyrazinyl.

7. A compound according to any preceding claim, wherein at least one L group is pyridinyl, oxadiazolyl, pyrazolyl, thiadiazolyl, pyrazinyl, benzofused thiazolyl, benzofused oxazolyl or benzofused imidazolyl, preferably at least one L group is pyridyl or pyrazinyl.

8. A compound according to any preceding claim, wherein $\mathbf{R_3}$ is phenylene or phenylene substituted with a halogen.

9. A compound according to any preceding claim, wherein at least one, preferably both, $\mathbf{R_2}$ is/are H.

10. A compound according to any preceding claim, wherein R' that is attached to L is independently selected from H, C_1-C_{10} alkyl or O-(C_1-C_{10} alkyl), halogen, C_1-C_{10} heterocycloalkyl, aryl, trifluoromethyl or heteroaryl.

11. A compound according to any preceding claim, wherein at least one R' is H, halogen, CF_3, C_1-C_6 alkyl, aryl optionally substituted with halogen, heteroaryl optionally substituted with halogen or heterocycloalkyl.

12. A compound according to any preceding claim, wherein at least one of the R' that is attached to L is heterocycloalkyl.

13. A compound according to claim 12, wherein R' attached to R_3 is hydrogen or halogen.

14. A compound according to claim 12, wherein at least one R' is C_1-C_6 alkyl optionally substituted with halogen, NH_2, $N0_2$ or hydroxyl.

15. A compound according to claim 14, wherein wherein at least one R' is C_1-C_6 alkyl optionally substituted with halogen.

16. A compound according to any preceding claim, as exemplified herein.

17. A compound according to any preceding claim, for use in therapy.

18. A compound according to any preceding claim, for use in the treatment or prevention of a condition mediated by histone deacetylase (HDAC).

19. A compound according to claim 18, wherein the condition is cancer, cardiac hypertrophy, chronic heart failure, an inflammatory condition, a cardiovascular disease, a haemoglobinopathy, a thalassemia, a sickle cell disease, a CNS disorder, an autoimmune disease, diabetes, osteoporosis, MDS, benign prostatic hyperplasia, endometriosis, oral leukoplakia, a genetically related metabolic disorder, an infection, Rubens-Taybi, fragile X syndrome, or alpha-1 antitrypsin deficiency.

20. A compound according to claim 18 or claim 19, wherein the condition is chronic lymphocytic leukaemia, breast cancer, prostate cancer, ovarian cancer, mesothelioma, T-cell lymphoma, cardiac hypertrophy, chronic heart failure, a skin inflammatory condition (in particular psoriasis, acne or eczema), a musculoskeletal inflammatory condition (in particular rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis or osteoarthritis), or an inflammatory condition of the gastrointestinal tract (in particular inflammatory bowel disease, Crohn's disease, ulcerative colitis, or irritable bowel syndrome).

21. A compound according to any of claims 1 to 16, for use in accelerating wound healing, protecting hair follicles, or as an immunosuppressant.

22. A pharmaceutical composition comprising a compound according to any of claims 1 to 16, and a pharmaceutically acceptable carrier or diluent.

23. A product containing (a) a compound according to any of claims 1 to 16, and (b) another inhibitor of HDAC, for simultaneous, separate or sequential use in the treatment or prevention of a condition mediated by HDAC.

24. A product containing (a) a compound according to any of claims 1 to 16, and (b) another chemotherapeutic or antineoplastic agent, for simultaneous, separate or sequential use in the treatment or prevention of cancer.

25. A method of treating a condition mediated by histone deacetylase (HDAC), comprising administering a pharmaceutically effective amount of a compound, composition or product according to any preceding claim.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2014/051454

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/14 C07D213/74 C07D401/12 C07D413/12
C07D417/12 C07D417/14 C07D495/04 C07D285/08 A61K31/4427
A61K31/4439 A61K31/501 A61K31/497 A61K31/506 A61K31/433

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2014	17/06/2014

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

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